Advanced Basal Cell Carcinoma:
Implications for Control and Treatment Through the Hedgehog Pathway

CME Learning Objectives

After reviewing the material, the participant should be able to:

• Review the clinical features and pathogenesis of basal cell carcinoma.
• Recognize patients with advanced basal cell carcinoma as well as treatment and monitoring needs specific to this population.
• Incorporate the most appropriate treatment regimens for advanced and metastatic basal cell carcinoma.
• Examine the hedgehog signaling pathway and evaluate emerging therapeutics that target this pathway in patients with advanced and metastatic basal cell carcinoma.

This continuing medical education activity is sponsored by

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Introduction

Basal cell carcinoma (BCC) is the most common human malignancy worldwide. Most BCC tumors are diagnosed early and effectively treated with available methods, ensuring an excellent prognosis. In contrast, locally advanced and metastatic BCC, although relatively uncommon, present a significant clinical challenge. For these patients, few effective management strategies are available, reflecting a lack of controlled clinical trials in this population. The prognosis for patients with metastatic BCC is poor, with a median survival of approximately 8 to 14 months, and a 5-year survival rate of only about 10%. Of relevance to these challenges, a growing body of recent evidence has demonstrated that the hedgehog intracellular signal transduction pathway is central to the development of BCC, and pharmacological inhibition of the hedgehog pathway represents a new and promising therapy for the treatment of advanced BCC.

Vindico Medical Education, in conjunction with HemOnc TODAY, sponsored a symposium in June 2012 to examine this new class of hedgehog pathway inhibitors for the treatment of locally advanced and metastatic BCC. A brief historical overview summarized the epidemiology, pathophysiology, clinical features, and impact of BCC, as well as the range of treatment options that are available. Presenters examined the particular challenges that are posed by advanced disease, including the limited therapeutic options and the lack of well-designed clinical research to guide decision making. Case studies were used to review some of the patient factors that contribute to advanced BCC, as well as the typical outcomes and limitations of treatment with historically available approaches. The hedgehog pathway in the development of BCC was examined and the results of recent clinical studies of hedgehog pathway inhibitors were reviewed.

This monograph, based on the material presented at the symposium, aims to provide health care professionals who manage BCC with a concise overview and update of emerging approaches to the management of locally advanced and metastatic BCC. I thank the speakers for sharing their knowledge, clinical experience, and perspectives on this important and challenging topic, and for participating in the preparation of this monograph.

Aleskandar Sekulic, MD, PhD
Course Chair
Basal cell carcinoma (BCC) is the most common malignancy in humans, accounting for more than 75% of newly diagnosed skin cancers. In contrast with many other solid tumors, patients with BCC often exhibit multiple primary tumors either simultaneously or at different times. BCC occurs at similar frequencies in men and women, with approximately 80% of lesions involving the head and neck. Estimates of BCC incidence vary from region to region, with reported incidence rates of 726 per 100,000 population in Australia, 500 per 100,000 in the United States, and 126 per 100,000 in Germany (personal communication with A Katalinic, MD, PhD, Germany). Approximately 1 million patients in the United States and 200,000 in Germany (personal communication with A Katalinic, MD, PhD, Germany) are diagnosed with BCC each year, although BCCs are not routinely registered and it is likely that published incidence rates significantly underestimate the actual number of individuals affected. Regardless of the precise number of individuals affected, it is clear that BCC represents a significant health problem for patients and for the health care system as a whole.

### BCC: Clinical Overview

Several clinical variants of BCC have been described. Superficial (multicentric, truncal) BCC, the most common type, is a well-circumscribed macule with minimal scale that is often found on the trunk or extremities. Nodular (cystic) BCC is characterized by a well-circumscribed single lesion with visible telangiectasia. Morpheaform (scar-like) BCC lesions are especially difficult to diagnose because they resemble normal scar tissue. Basosquamous (metatypic) BCC exhibits features of both BCC and squamous cell carcinoma (SCC), tends to be especially aggressive, and is associated with a high risk of metastasis. Other BCCs that are associated with aggressive growth patterns include infiltrative or micronodular BCC. In addition, pre-existing skin lesions known as sebaceous nevi may be associated with proliferation of basaloid cells and transformation to BCC.
Ultraviolet (UV) radiation exposure is clearly a risk factor for BCC, although the pathophysiology of BCC is complex, and many other risk factors have been identified (eg, individual genetic factors, topical nitrogen mustard exposure, burn scars). Both cumulative and intermittent high-intensity UV exposure are associated with increased BCC incidence, and this relationship is modulated by skin type.\(^8\)\(^9\) BCC is observed more often in individuals with fair skin rather than dark skin and blacks with albinism are at extremely high risk.\(^10\) Environmental factors, such as outdoor work, are linked to increased UV exposure. For example, a recent study in Germany found that outdoor workers had an 18% relative increase in the risk of BCC, and a 52% relative increase in the risk of SCC.\(^11\) Although less true today, arsenic exposure was historically a common cause of BCC. The risk of BCC is also linked to immunosuppression, including immunosuppression associated with some tyrosine kinase inhibitors.\(^12\) Epidermal DNA damage in individuals who are deficient in DNA repair enzymes is associated with basal cell nevus syndrome (BCNS) (also referred to as Gorlin-Goltz syndrome, xeroderma pigmentosum, and BCC syndrome), a condition that is characterized by a high risk of multiple BCCs even in childhood.\(^13\) BCNS is an autosomal dominant disorder with a prevalence of approximately 1:56,000, which manifests at an early age.\(^14\) The pathology of BCNS involves mutation of the Patched (\textit{PTCH}) tumor suppressor gene located on chromosome 9.\(^15\) In Drosophila, \textit{PTCH} is important in the growth and regulation of segmental development; in humans, it is important for cell differentiation and division in skin and teeth during development.\(^16\) BCNS is characterized clinically by multiple BCCs, palmar-plantar pits, odontogenic keratocysts, and skeletal abnormalities (calcifications).\(^17\) These patients may exhibit dozens of excision sites and new lesions, many of which are only millimeters in diameter. Other common characteristics include calcification of the falx cerebri and bridging of the sella turcica.\(^18\) BCNS is also associated with ovarian fibromas (rarely transforming into fibrosarcomas), which occur in approximately 75% of female patients,\(^19\) and medulloblastomas, which occur in approximately 5% of patients of both genders.\(^19\) Other clinical features vary according to the specific \textit{PTCH} mutations observed.

Metastatic BCCs are typically tumors that have been misdiagnosed or neglected (eg, in patients with severe underlying disease, older age, history of alcohol abuse, or other barriers to care). Locally advanced BCCs have been estimated to account for approximately 1 in 50 to 1 in 100 of all diagnosed BCCs. The incidence rate is influenced by socioeconomic factors and region. For example, individuals in areas that are less economically developed have less access to health care and are more likely to neglect early BCC, increasing the likelihood of eventual advanced disease. Metastatic BCC is a rare disease, with reported incidence rates ranging from 0.0028% to 0.5% of the population.\(^20\) although it is possible that metastatic BCCs are under-reported.

**BCC Treatment**

Treatment decisions are driven by the clinical pathological appearance of the lesion (eg, depth of tumor infiltration into the skin). The principal approach to the treatment of BCC usually involves total removal or destruction of BCC with preservation of normal tissue and optimal aesthetic results (cosmesis). The goals for patients with locally advanced, inoperable, or metastatic tumors include palliation of symptoms or the use of neoadjuvant treatment to decrease the tumor size before surgery. For advanced and metastatic BCCs, combination therapy with surgery and radiation is an option for a small number of patients. Palliation with platinum-based chemotherapy generally consists of the same regimens that are used to treat advanced SCC.\(^21\) The hedgehog pathway inhibitor vismodegib is a new treatment option for patients with advanced BCC.\(^22\) Treatment of superficial BCCs is typically surgical excision, which offers the advantage of histologic control. Micrographic (Mohs) surgery is performed for morpheic, aggressive, and recurrent BCCs and is especially common in the United States. Cryosurgery is an alternative to conventional surgical excision but does not provide the option of histologic control. Other options for superficial lesions include radiation therapy, laser therapy, and topical fluorouracil (5-FU).\(^23\) Photodynamic therapy is an approved treatment alternative only for superficial BCC. Similarly, the topical immune response modifier imiquimod is approved only for superficial disease and not for nodular lesions. For aggressive BCCs, surgery is the mainstay of treatment, with a goal of achieving histologic control of the deep and lateral tumor margins. Radiotherapy may be appropriate for elderly patients, although a disadvantage is that it is a blind treatment technique. A recent literature review examined treatment outcomes for
patients with metastatic BCC using articles published between 1981 and 2001. Only cases with reported survival data and confirmed histologies from the primary tumor and metastatic sites were selected for this analysis. A total of 100 cases were identified that met inclusion criteria, including 38 patients with local lymph node metastases (LNM) and 62 patients with disseminated metastases (DM). The male:female ratio was 2:1. Twenty of the patients had received chemotherapy, which usually consisted of platinum-based regimens. The duration of survival varied from 0 months to more than 120 months. The one-year survival rate was 73.2% (86.5% for patients with LNM only, and 64.9% for those with DM).

Summary and Conclusions
Locally advanced and metastatic BCC are uncommon and typically reflect tumors that have been neglected or misdiagnosed. Although there are a number of treatment options for patients with superficial BCCs, advanced BCC presents a significant treatment challenge. Inhibition of the hedgehog cell signal transduction pathway has recently emerged as a new treatment option for patients with locally advanced or metastatic BCC.

References

Full references are available at www.healio.com/hematology-oncology/education-lab.
Advanced Basal Cell Carcinoma: Case Presentations

Karl D. Lewis, MD

Advanced basal cell carcinoma (BCC) is a difficult-to-treat condition with few effective management options. BCCs are believed to arise from keratinocytes of the basal layer of the epidermis (Figure). The absorption of ultraviolet radiation by DNA produces a mutagenic effect that increases the risk of skin cancers, including BCC. This effect is countered by melanin, which absorbs ultraviolet radiation in the same portion of the spectrum as DNA. Thus, individuals with fair skin have little natural protection against UV-induced DNA damage, and are at increased risk of BCC as a consequence of sun exposure. Low-risk BCC lesions may be treated using cryosurgery, electrodessication, or topical therapy with 5-fluorouracil (5-FU) or imiquimod. High-risk lesions are treated using surgical excision, Micrographic (Mohs) surgery, or radiation therapy. Although BCCs generally have a low metastatic potential and are typically viewed as a relatively minor health threat, they can be locally aggressive and cause destruction of skin and surrounding structures. The following case studies describe some of the challenges associated with treatment of these advanced lesions.
Case Study 1
The patient is a 73-year-old male and retired engineer with a long history of BCC. In 1980, a BCC was resected from the bridge of his nose near the medial aspect of his right eye. Over the following several years he had many recurrences that required subsequent surgical resections. In 1999, he required radical resection with removal of nasal and frontal bones, and he continued to develop further BCC recurrences. In 2006, a recurrence in the right orbit led to loss of vision. He refused radiation or further surgery. By 2009, continued growth of the mass began to cause severe headaches, which prompted representation for medical care. Imaging demonstrated a large enhancing mass within the orbit extending into the anterior cranial fossa. The tumor mass was associated with bone destruction and compression of the patient’s frontal lobes. This patient’s BCC represents a significant clinical challenge with few favorable treatment options.

Case Study 2
The patient is a 67-year-old woman with a long history of recurrent BCC. She had previously been treated for locally advanced and recurrent BCC of the left nares, and had undergone numerous surgical procedures including Mohs surgery and a large reconstructive procedure that required a forehead flap. She presented to the clinic in 2008 with recurrent BCC. There were no systemic therapy options or clinical trials at that time, and treatment recommendations included additional surgery and radiation therapy. She presented again in 2010 with recurrent disease and a large open wound involving the bridge of the nose. Biopsy of the septum confirmed that she had recurrent BCC.

Case Study 3
The patient is a 68-year-old man with multiple locally advanced BCCs. In 2006, he presented to his primary care physician with lesions involving the scalp, right temple, and mid-forehead. Biopsies of the lesions were obtained and all were pathologically consistent with BCC. He did not receive follow-up care at that time. His lesions grew over the next several years, and during 1 to 2 years before representation for care, the scalp lesion continued to exude moisture slowly and occasionally bleed. He experienced severe headaches and progression of the lesion on his temple caused retraction of the right eyebrow. At presentation, he had a large, neglected, unresectable lesion involving his forehead, as well as many other lesions involving his cheek, ear, eyebrow, and other sites.

Discussion
The first case of metastatic BCC in the medical literature was reported in 1894. Since that time, approximately 300 cases have been reported. An accurate determination of the incidence of advanced BCC has been difficult to obtain because there are no acceptable patient registries. Estimated rates reported in the literature have varied from 0.0028% to 0.55%, although these estimates were made many decades ago and are based on findings from single institutions. The lower estimated incidence rate would translate to an incidence of 1 in 35,000 patients with metastatic BCC in the United States, which seems high considering the small number of reported cases in the medical literature.

As noted previously, treatment options for patients with BCC include cryosurgery, electrodessication, topical therapy, surgical excision, MOHS surgery, and radiation therapy. None of these are favorable options for patients with advanced BCC, who have large lesions with extensive destruction of overlying skin. Medical oncologists have historically had a relatively minimal role in the treatment of BCC, and no prospective clinical trials have demonstrated a significant beneficial effect of any chemotherapy drug in this patient population. Chemotherapy for metastatic BCC has been described in case reports using many different agents, including cyclophosphamide, etoposide, 5-FU, methotrexate, bleomycin, doxorubicin, cisplatin, carboplatin, and paclitaxel. Cisplatin, alone or in combination, may be the most effective chemotherapy strategy for patients with metastatic BCC. In one review of 12 patients with BCC who were treated with platinum-containing regimens, 5 patients exhibited complete responses, with durations of response of 3 to 18 months; 4 patients exhibited partial responses, and 3 patients had stable disease. Results of targeted therapy have been reported in a small number of case studies. Two case reports described the use of the cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR) for the treatment of locally advanced or metastatic BCC. One patient with locally advanced BCC responded to treatment, and 2 patients who failed to respond to chemotherapy had stable disease. Until recently, treatment guidelines from the National Comprehensive Cancer Network (NCCN)
recommended enrollment in a clinical trial of a hedgehog pathway inhibitor for patients with metastatic BCC. Recently revised guidelines now recommend consideration of a clinical trial (preferred) or the hedgehog pathway inhibitor vismodegib for patients with regional or distant metastases.\textsuperscript{15}

Chemotherapy options for locally advanced BCC are similar to those for metastatic disease. Case reports have described the use of chemotherapy for the treatment of locally advanced BCC in 16 patients, most of whom were treated with platinum-containing regimens.\textsuperscript{12,16} The overall response rate was 75%, including 8 complete responses and 4 partial responses. Although these observations provide some support for the use of chemotherapy for the treatment of locally advanced or metastatic BCC, case reports are associated with many important limitations. Treatment regimens vary considerably in cytotoxic agents, drug doses, administration schedules, and timing of assessments. Results may be influenced by selection bias, as there may be important reasons why patients were selected to receive or not receive a particular treatment. In addition, investigators are much more likely to report results of positive treatment responses than patients who were treated but who did not respond, rendering it difficult to estimate true treatment response rates. Finally, case reports do not use standardized response evaluations across studies, which further complicates efforts to determine the true response rate with chemotherapy.

Summary and Conclusions
Locally advanced and metastatic BCC, although uncommon, are significant clinical problems. Historically, medical therapy (and, therefore, medical oncology) has played a small role in the management of BCC. Cisplatin-containing chemotherapy regimens are probably active against advanced BCC, but there are no clinical trial data to guide decision-making. More effective medical therapies are clearly needed for patients with advanced BCC.

References

Full references are available at www.healio.com/hematology-oncology/education-lab.
Targeting the Hedgehog Signaling Pathway for Treatment of Basal Cell Carcinoma

Aleksandar Sekulic, MD, PhD

Although most basal cell carcinomas (BCCs) are curable by surgery or radiation therapy, some patients progress to locally advanced or metastatic disease. Currently, there are no adequate standard-of-care treatments for patients with advanced BCC, and there is a considerable need for new treatment options for these patients. Recent research has examined the role of the hedgehog signal transduction pathway in the pathogenesis of BCC, and the efficacy and safety of hedgehog pathway inhibitors in BCC treatment. When evaluating treatment response rates in clinical studies of investigational agents, it is important to consider that these patients have already failed to respond to conventional methods of treatment that are normally associated with high success rates.

The Hedgehog Pathway

Research linking the hedgehog signal transduction pathway with embryonic development began with the observation that congenital cyclopia was endemic among lambs born in the western United States in the early 20th century. Although the cause was initially unknown, cyclopia was eventually linked to the ingestion of the corn lily plant by pregnant ewes. Interestingly, although ingestion of corn lily was shown to induce fetal malformations when consumed during pregnancy, there were no discernible effects of the plant on adult animals. Analysis of plant extracts led to the identification of the alkaloid molecule cyclopamine, which was subsequently shown to induce teratogenic effects by inhibiting the hedgehog signal transduction pathway, which is critical for normal embryonic development. The key component of this pathway is the transmembrane protein Smoothened (Smo), which has an inherent tendency to activate a proliferative signal within the cell unless it is inhibited by a second transmembrane protein, Patched (PTCH). When PTCH binds to its extracellular ligand – the hedgehog protein – the repression of Smo is released, and an intracellular growth signal is initiated. The hedgehog pathway is inappropriately activated in more than 90% of BCC tumors, either through activating mutations in Smo that render it less susceptible to inhibition by PTCH, or by mutations that lead to decreased PTCH expression. In either case, unopposed activity of Smo results in increased cellular proliferation. This signal transduction pathway, in which aberrant activation of a single protein results in virtually all BCCs, creates a uniform point of therapeutic vulnerability in this cancer. The development of targeted Smo inhibitors, such as vismodegib (GDC-0449), has made it possible to interrupt this pathway and improve clinical outcomes for patients with this common malignancy.

Topical and Systemic Hedgehog Pathway Inhibitors

The development of Smo inhibitors for cancer therapy began with the recognition that cyclopamine, which binds directly to Smo and inhibits activation of the hedgehog pathway, also prevents the growth of cancer cells in tissue culture. Vismodegib is approved for the treatment of locally advanced or metastatic BCC, whereas several other hedgehog pathway inhibitors are being evaluated in phase 1 and phase 2 clinical trials for BCC and other solid tumors.

The first topical Smo inhibitor, CUR61414, produced high tissue penetration and tumor responses when evaluated in a murine BCC model. Topical application of CUR61414
significantly decreased expression of GLI1, a transcription factor and oncogene protein product that is normally up-regulated by activation of the hedgehog pathway. However, in a phase 1 clinical trial in human patients with superficial or nodular BCC, topical application of CUR61414 did not affect GLI1 expression or lesion size. From this study, it is unclear whether the lack of effect in human subjects reflected limited skin penetration, drug clearance, or species specificity. A second topical Smo inhibitor, LDE225, was evaluated in a phase 2 clinical trial in which patients with nevoid basal cell carcinoma syndrome (NBCCS) applied either 0.25% or 0.75% topical LDE225 cream twice daily for 4 weeks. Of 13 lesions treated with topical LDE225 at the 0.75% concentration, 3 lesions exhibited complete response, 9 exhibited partial response, and 1 exhibited no response. In contrast, of 14 lesions treated with vehicle cream, 1 exhibited partial response and 13 exhibited no response (Figure 1).

The efficacy of systemic hedgehog pathway inhibition for BCC was first demonstrated in a phase 1 clinical trial, the results of which were published in 2009 in the New England Journal of Medicine. In this study, 33 patients with locally advanced or metastatic BCC received oral vismodegib at 1 of 3 doses: 150 mg per day (n=17), 270 mg per day (n=15), or 540 mg per day (n=1). Objective responses were noted for 18 of 33 patients (55%) who received vismodegib, including 2 complete responses and 16 partial responses. The remaining patients had stable disease (11 patients) or disease progression (4 patients). A subsequent report from this study described a treatment response in one additional patient, for an overall response rate of 58%. The median duration of response was 12.8 months. The most common adverse events with vismodegib were fatigue, altered taste, anorexia, weight loss, muscle spasm, and hair loss. No dose-limiting toxicities or grade 5 adverse events were observed during the study period. One patient developed a grade 4 adverse event (asymptomatic hyponatremia).

These promising initial observations provided the foundation for the pivotal phase 2 ERIVANCE

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**Table. Hedgehog Inhibitors in Clinical Development for Basal Cell Carcinoma or Other Cancers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Trials</th>
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<tr>
<td>GDC-0449 (Vismodegib)</td>
<td>FDA-approved</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LDE225</td>
<td>Investigational</td>
<td>Phase 2</td>
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<td>LEQ506</td>
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Source: Clinical trial search in May 2012; Clinicaltrials.gov.

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**Figure 1. Clinical Response with Topical LDE225 vs. Vehicle in Patients with Nevoid Basal Cell Carcinoma Syndrome**

BCC clinical trial, which was designed to more definitively evaluate the efficacy of vismodegib. Patients with histologically confirmed, radiologically measurable metastatic BCC or locally advanced BCC were treated with vismodegib 150 mg daily until disease progression, intolerable toxicity, or withdrawal from the study for other reasons. The primary endpoint was the overall response rate, which was determined by an independent review facility that was provided with patient photographs and imaging results. In the metastatic cohort, treatment response was defined using conventional Response Evaluation In Solid Tumor (RECIST) imaging criteria as a reduction in tumor size of at least 30% from baseline. In the locally advanced cohort, response was evaluated using a novel composite endpoint that included measurable lesion diameter, tumor ulceration, and RECIST measures of the deeper tumor components (when present). Using this composite measure, treatment response was defined as a decrease in tumor size of at least 30% by physical examination and imaging (CT or MRI, or both), in patients with deep tissue involvement, as well as complete resolution of ulceration. Disease progression was defined as an increase in tumor size of at least 20% in patients with metastatic BCC and by either an increase in size of at least 20% or the presence of new lesions or ulcerations in patients with locally advanced BCC. The median age of patients in both the metastatic and locally advanced cohorts was 62 years, with a range from 21 to 101 years. Approximately 60% of the patients were male, and all were white. For patients with locally advanced disease, 38.1% were inoperable; for the remaining 61.9%, surgery was considered inappropriate due to multiple recurrence or significant morbidity or deformity.

In the metastatic BCC cohort, a treatment response was noted for 10 of 33 (30.3%) patients by the interferon regulatory factor (IRF) (the study primary endpoint) and for 15 patients (45.5%) by investigator assessment (a secondary endpoint). The median duration of response was 7.6 months for the IRF assessment and 12.9 months for the individual investigator assessment. Lesion diameter decreased from baseline for most patients and a tumor reduction was noted for all patients considered treatment responders by IRF assessment. This investigator-rated reaction rate was similar
to the response rate in the phase 1 study described previously. The median duration of response was 7.6 months by both IRF and investigator assessments. Most patients exhibited more than 50% reduction in lesion size from baseline (Figure 2). In both the metastatic and locally advanced cohorts, the median progression-free survival was 9.5 months. The clinical benefit rate, which was defined as the number of patients with response at any time or stable disease, was 76% of patients in the metastatic cohort and 75% in the locally advanced cohort. For the 104 patients in both cohorts combined, serious adverse events were noted for 26 patients (25%), and were considered possibly related to vismodegib in 4 patients (4%). Seven patients died during the course of the study, although none of the deaths were considered to be related to vismodegib treatment. The most common adverse events included muscle spasms, alopecia, altered taste, weight decrease, fatigue, nausea, decreased appetite, and diarrhea.

An oral formulation of LDE225 was examined in a phase 1, open-label, 2-part clinical trial that enrolled 76 patients with advanced solid tumors.13 In the dose-escalation phase of the study, patients received increasing doses of LDE225 to determine a maximum tolerated dose. Dosing began at 100 mg once daily, and was gradually escalated to a maximum of 3,000 mg once-daily or 750 mg twice-daily. In the expansion phase of the study, this maximum tolerated dose was administered once daily for 28 days. Treatment was well tolerated at daily doses of up to 800 mg. Of 6 patients with BCC who received LDE225 at the 800 mg per day dose for long enough to evaluate response to therapy, the overall best responses were partial response in 3 patients, complete response in 1 patient, and stable disease in 2 patients. Partial responses were also noted in 2 patients with medulloblastoma. Adverse events of LDE225 were similar to those of vismodegib, and included altered taste, muscle spasms, alopecia, weight loss, and elevated blood creatine phosphokinase (CPK). The similarity of the adverse events profile between vismodegib and LDE225 indicates that some of the adverse events represent a drug class effect, as would be expected in light of the well documented role of hedgehog pathway in normal cellular processes, including hair growth or taste bud maintenance.

The development of effective approaches for management of adverse events occurring in context of hedgehog pathway inhibition is of particular clinical relevance. This is illustrated by muscle cramps, which can be especially challenging. Our clinical experience suggests that a stepwise management approach may be helpful in this scenario with the first-line option being calcium, magnesium, and potassium supplementation. If supplementation does not provide adequate control of symptoms, other options include muscle relaxants or gabapentin. If cramps cannot be controlled with medical therapy, it may be necessary to temporarily suspend treatment (drug holiday).

Summary and Conclusions

Targeted Smo inhibition provides substantial clinical benefit for patients with locally advanced or metastatic BCC. Common adverse events are likely class-related. One Smo inhibitor, vismodegib, is now FDA-approved for patients with locally advanced or metastatic BCC. The effects of the Smo inhibitor cyclopamine on fetal development in sheep demonstrate that Smo inhibitors must not be used by pregnant patients, and that they must be used with extreme caution in women of childbearing potential.

References


Full references are available at www.healio.com/hematology-oncology/education-lab.
Beyond Advanced BCC: Targeting the Hedgehog Signaling Pathway for BCC Prevention

Jean Y. Tang, MD, PhD

Although surgical resection of basal cell carcinoma (BCC) is often curative, surgical scarring and other complications are associated with significant morbidity, and there are no effective preventive approaches. Nearly all BCCs exhibit gene mutations that result in abnormally elevated activity of the hedgehog signal transduction pathway, usually involving mutational inactivation of the tumor-suppressing protein Patched (PTCH) gene.¹ Patients with basal cell nevus syndrome (BCNS) have PTCH mutations and a clinical presentation that is characterized by numerous BCC lesions.² Although surgical treatment of a single BCC is usually not difficult, recurrence following surgery is common. Individuals with BCNS therefore present a significant treatment challenge, and new approaches are needed to provide better long-term tumor control for these patients. Topical approaches have included the immunosuppressant imiquimod and the chemotherapy agent 5-fluorouracil (5-FU). These agents may be effective for superficial BCCs, but are not useful for nodular, infiltrative, or morpheic subtypes. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) or oral retinoids, although effective against BCC in animal models, were of limited effectiveness in clinical trials.³⁴ The topical retinoid tazarotene has been reported to improve BCC lesions,⁵ and is being evaluated for the treatment of BCCs in patients with BCNS who are undergoing organ transplantation. Photodynamic therapy is effective for the treatment of smaller lesions but not for the numerous large, nodular, deep lesions that are characteristic of most patients with BCNS.

Vismodegib for the Treatment and Prevention of BCNS

Vismodegib is an oral small-molecule inhibitor of the hedgehog signaling pathway molecule Smoothened (Smo). The effectiveness of vismodegib for the prevention and treatment of new BCCs was examined in an investigator-initiated, randomized, double-blind clinical trial of 41 patients with BCNS.⁶ Patients were enrolled at 3 clinical centers between September 2009 and December 2010, and were randomized to treatment with vismodegib 150 mg (n=26) or placebo (n=18) for 18 months. The primary endpoint was the prevention of new BCCs; secondary endpoints included reduction in size of existing BCCs and assessment of safety and tolerability. The vismodegib and placebo groups were similar at baseline in terms of mean age (54 vs. 53 years for the vismodegib and placebo groups, respectively), percentage of female patients (30% vs. 40%), and number of BCCs at baseline (29 vs. 27). The average duration of follow-up was 9 months for the vismodegib group and 7 months for the placebo group. During this period, the investigators identified a total of 2,000 existing BCC lesions and 694 new lesions, confirming the very high burden of disease in these patients.

The cumulative number of new surgically eligible BCCs (nSEB) was lower for patients who received vismodegib compared with those receiving placebo (Figure 1). At the recommendation of the Data Safety and Monitoring Board, the placebo arm was discontinued.

Figure 1. Cumulative Number of New Surgically Eligible BCCs (nSEB)

Vismodegib prevented new surgically eligible BCCs (nSEB) in patients with basal cell nevus syndrome.

because it was considered unethical to continue treating patients with placebo. The annualized number of new BCCs was significantly lower for patients randomized to vismodegib vs. placebo (2 vs. 29 new BCCs per year; \( P < .001 \)). In addition, vismodegib significantly reduced the size of existing tumors during a follow-up period of up to 15 months, whereas tumor size remained constant or increased for patients randomized to placebo (Figure 2). Clinically significant improvement was noted for deep nodular lesions, including lesions in locations that are often difficult to manage surgically (eg, near the eyes or nose). Improvement was also noted for palmar/plantar pitting, which is common in patients with BCNS and often significantly diminishes patient quality of life. Histologic examination of residual BCC at sites of clinically evident tumor clearing demonstrated histologic clearance (ie, no residual tumor cells) in 34% of biopsy samples, which were obtained between 1 and 9 months after beginning treatment. GLI1 gene expression, a downstream target of hedgehog pathway activation, was significantly decreased after 1 month in the vismodegib group but not in the placebo group, suggesting that the effects of vismodegib on BCC formation reflect on-target inhibition of the hedgehog signaling pathway. Adverse events that were significantly more common with vismodegib than placebo included taste disturbance, weight loss, muscle cramps, and hair loss. Most adverse events were of grade 1 or grade 2 severity, and no patients died or required hospitalization due to adverse events.

Although the study design assumed that treatment with vismodegib for up to 18 months may be required to produce a significant anti-tumor effect in patients with BCNS, a significant reduction in BCCs was observed after only 1 month of treatment. However, treatment-related adverse events limited the ability of patients to remain on long-term vismodegib treatment. BCCs gradually returned in patients who discontinued study medication, approaching baseline lesion severity over a period of approximately 6 months. In many cases, the sites of BCC recurrence were identical to the patients’ initial lesion sites. These results suggest that hedgehog pathway inhibition with vismodegib suppresses BCC formation but that this treatment does not cure patients with BCNS.

**Summary and Conclusions**

Once-daily oral vismodegib rapidly shrinks existing BCCs and prevents new lesions in patients with BCNS. Adverse events were generally mild to moderate in severity and were reversible with drug discontinuation, but pose a challenge to long-term treatment for some patients. Resolution of muscle cramping generally occurs within 2 weeks of treatment discontinuation, and taste disturbance resolves within 1 month. Hair loss abates after approximately 2 months, and hair quality and texture are eventually quite similar to baseline. No drug resistance has been observed among the approximately 2,000 tumors treated, although BCCs return after vismodegib discontinuation. A second clinical trial has recently begun to examine whether an intermittent vismodegib dosing regimen (eg, alternating cycles of 2 months on treatment followed by 2 months off treatment) will provide greater tolerability and improve the ability of patients to remain on treatment for longer periods of time. Possibly extended vismodegib, or the combination of vismodegib with other therapies, might yield a sustainable cure for BCC. Finally, it should be noted that vismodegib is approved for the treatment of advanced BCC, and is not approved for superficial BCC or for patients with BCNS.

**References**


Full references are available at www.healio.com/hematology-oncology/education-lab.
DISCUSSION

Are patients with basal cell carcinoma (BCC) at increased risk of other malignancies as a result of these hedgehog pathway mutations?

Jean Y. Tang, MD, PhD: Patients with basal cell nevus syndrome (BCNS) are at higher risk for medulloblastomas and rhabdomyoma sarcomas. For other cancers that are driven by the hedgehog signaling pathway, researchers have so far identified subsets of pancreatic, small cell lung, breast, and gastrointestinal tumors and there are many clinical trials investing the use of these novel Smoothened (Smo) antagonists for these other cancers.

Have quinines been used for cramps, and are they effective? Also, is dose reduction an option for these patients?

Karl D. Lewis, MD: We have not used quinine for cramps. In the clinical trial, electrolyte supplementation was not effective. What was most effective were drug holidays. If you suspend treatment for a few weeks, their symptoms abate rather quickly, and treatment can be resumed, which is why the intermittent dosing schedule is of much interest. Regarding dose modification, the drug is approved at a dose of 150 mg daily with no recommendations for dose reduction.

Do patients respond to retreatment?

Tang: So far, everything we have seen indicates that patients do respond to retreatment. We have put a patient on treatment 3 times after several drug holidays. There is a potential concern about drug resistance. One way to cause resistance is lowering the dose of the drug such that it is not completely effective. Another way may be excessive use of intermittent treatment. Efficacy has to be balanced with tolerability while also watching out for resistance.

Can radiation therapy cause basal cell carcinoma?

Axel Hauschild, MD: There are examples of this with radiation therapy, especially in children. There was a case in Essen, Germany, in which a girl underwent radiation therapy of the neck for lymphoma. She had no known history of BCNS, but after radiation, she developed approximately 100 basal cell carcinomas (BCCs) in the radiation field. Radiation is effective for the treatment of BCCs, but it is a contraindication for BCNS because these patients are more likely to develop BCCs. In general, in radiation scars not only squamous cell carcinomas (SCCs), but also BCCs can arise. Another tumor that is rarely observed is angiosarcoma.

Are there any proposed mechanisms to account for vismodegib resistance?

Aleksandar Sekulic, MD, PhD: The data are incomplete. In patients with multiple small BCCs, there does not seem to be resistance. In the patients with locally advanced or metastatic BCC, there have been some patients who have not responded as well as others, and the issue of primary resistance vs. potential secondary resistance is not yet understood. There are mechanisms that have been observed in medulloblastoma. There are mutations that render Smo insensitive to the drug. There are other mechanisms, such as upregulation of downstream components in the hedgehog pathway, as well as activation of some autocrine regulatory loops through growth factors that have been postulated. However these are preliminary observations.

At what age do BCNS patients begin manifesting basal cells?

Tang: Almost all BCNS patients have mutations in PTCH1, but the expression or the phenotype is quite variable. So it depends on the mutation and how early the patient get the basal cells. Most BCNS patients have their first BCC in adolescence or early 20s. In fact, that is one of the criteria for diagnosis. However, the first clinical presentation is not necessarily the BCC, because in their adolescence or during childhood they may have developed jaw cysts. So in many cases, the diagnosis is made by an oral surgeon or dentist, and not necessarily by the dermatologist.

For patients with BCC who respond but who continue to have large nonhealing skin defects, have you ever tried to promote healing with hyperbaric oxygen?

Hauschild: I have not, but we had a marine institute in Kiel, Germany that was providing hyperbaric oxygen for the German Navy. The results are not convincing. There were also trials 15 to 20 years ago, where the results were not convincing. What is needed is secondary plastic reconstruction of those defects that were treated, particularly with vismodegib, and there needs to be confirmation that there is a complete regression of the lesion before the patient is sent to the plastic surgeon. Patients with advanced BCC need to be discussed in an interdisciplinary roundtable. This is not only a tumor for medical oncologists or for dermatologists, it is a tumor that needs to be discussed with everyone who is able to provide knowledge on the tumor, including ear, nose, and throat, maxillofacial surgery, or plastic surgery.

Is there any response to vismodegib in patients with SCC?

Tang: Vismodegib is not effective in the treatment of SCC. The pathophysiology of SCC is more complex, and it is not driven by the hedgehog signaling pathway. In some of the clinical trial patients who had a tumor with mixed histology—that is, a basal component and a squamous component—vismodegib shrunk the basal cell component without affecting the squamous cell component.
DISCUSSION

Hauschild: A few patients in the ERIVANCE trial had basosquamous differentiation of their tumors or metatypical BCCs. To my knowledge, these patients who are typically considered ineligible for clinical trials showed the same response rate to vismodegib.

Does inhibition of Smo by vismodegib have implications in other cancers besides BCC?

Lewis: Medulloblastoma also exhibits PTCH mutations and has been shown to respond to hedgehog pathway inhibition. Some researchers have proposed a stem cell effect in other tumor types, such as pancreatic cancer. However, these mutations may not occur at the same frequency as they do in BCC, and it is unlikely that medulloblastoma will respond to the same degree.

What causes sporadic PTCH1 mutations?

Tang: PTCH1 mutations probably occur through UV exposure. In fact, there are data linking mutations in PTCH1 with UV signatures associated with sun-induced DNA damage. The most common cause is therefore sunlight.

There are case reports in the literature of dramatic responses of patients with BCC treated with taxane-based chemotherapy. Do you have any experience treating metastatic or locally advanced BCC with taxane-based chemotherapy?

Lewis: No. The problem with the literature is that chemotherapy results have been reported on a case report basis only. So at this point, it is impossible to know the true response rate to taxane-based chemotherapy. Even though I am part of the Cutaneous Oncology Clinic at the University of Colorado, I rarely saw patients in this situation until we had the hedgehog inhibitors. They just did not come to our clinic because there were no effective therapies. Once we started to evaluate the hedgehog inhibitors – which we have been involved with since phase 1 – we have seen more patients. Most of the experience we have in treating advanced disease is with hedgehog inhibitors.

Does hair loss happen in all patients? Is hair loss complete or partial, and are there any prophylactic treatments to prevent hair loss?

Tang: Unfortunately, there is nothing to prevent the hair loss. The hair seems to fall out in the telogen cycle. We have collected bags of hair on all of our patients, and we are in the process of describing the hair loss. Many of our patients do not mind wearing an attractive wig. Importantly, when the therapy is stopped, the hair does grow back.

How long should a patient with BCC be treated?

Sekulic: We have seen data from patients with BCNS demonstrating that these tumors will recur in many cases after they are treated. We do not know whether that applies to sporadic basic cell carcinomas, and we also do not know which sporadic BCCs that may apply to. There is an ongoing phase 2 clinical trial that we are now conducting that is examining operable BCCs. A cohort in that trial is being treated and then observed for six months. The timing of tumor recurrence will be observed over the coming years, as the recurrence may be delayed, given the slow-growing nature of many of these tumors.

How do you define stable disease in metastatic BCC, considering the slow-growing nature of this tumor? What would be your recommendations for staging intervals?

Sekulic: This is a very good point because in many of these cases, if the tumor is slow-growing, one has to think about the rate of growth, and observation over a period of time would be associated with tumor growth even if you were not treating. This also varies from case to case. Close observation, with clinic visits every 4 weeks and imaging every 8 weeks, may be too soon for many patients, it depends on the individual patient.

Do BCC cells that are exposed to hedgehog pathway inhibition die by apoptosis or necrosis?

Tang: We performed biopsies after 1 month of vismodegib treatment, and we did not detect any evidence of apoptosis as measured using Cleaved Caspase-3. However, apoptosis is an early response, and so we may have missed the time period in which it occurs. With LDE255,
biopsy at an earlier time point did reveal evidence for inhibition of hedgehog signaling leading to increased apoptosis. Histologically, there is evidence for both apoptosis and necrosis.

**Do we need to test BCCs before treating them with hedgehog inhibitors?**

**Hauschild**: The rate of mutations is extremely high even in spontaneous BCCs, and I am not aware of anyone who advocates testing before treatment. Retesting a patient who does not respond to hedgehog inhibitor therapy may be useful to evaluate whether the patient has primary or secondary resistance, but I do not believe it leads to a different treatment decision. In addition, mutations other than *Smoothened* and *PTCH1* play a role in the development of BCCs, and particularly BCNS.

**Sekulic**: I would. This was studied years ago with p53 mutations, which are also very common in these tumors.

**What are your thoughts on using vismodegib in treatment of local BCC?**

**Sekulic**: This is being investigated in a clinical trial that I mentioned earlier, which is examining vismodegib for local, operable, nonadvanced BCCs. This study is examining the histology of how these tumors shrink, and whether they recur after they have resolved.

**Hauschild**: A patient with a high number of BCCs, which are in principle operable, could be a good candidate for vismodegib. However, I would like to emphasize that a patient, who has just one operable BCC and is afraid of surgical intervention is not the best candidate for systemic treatment with vismodegib, simply because it causes side effects. These patients who do not want to be operated on are also cautious when they hear about potential adverse events. I strongly believe that a relatively simple surgical excision of a small BCC is a better option than a relatively long systemic treatment with unpredictable side effects.

**How long does dysgeusia continue after stopping vismodegib treatment? Also, what is the reversibility of hair loss?**

**Tang**: Taste disturbance usually resolves in 3 to 4 weeks, and eventually returns to baseline levels. Hair loss also stops at 1 month, with regrowth over several months afterwards. The quality of hair also returns to baseline.

**What is the response rate in BCNS with vismodegib? Is the time to respond similar following a drug holiday?**

**Tang**: Regarding the time to respond after a treatment holiday, there is not enough data to draw firm conclusions. Oncologists classify treatment response in various ways, such as complete response, partial response, stable disease, or progressive disease. Patients with BCNS have multiple lesions rather than a single target tumor. Data have been presented as cumulative tumor burden, but typical practice is to track individual lesions. We have not calculated response rates using Response Evaluation Criteria in Solid Tumors (RECIST) criteria for our individual patients. I would estimate that of the 41 patients we have treated, more than half have attained a complete or partial response by RECIST criteria because their tumor diameters have decreased by more than 30%.

**Is it possible to have elevated hedgehog ligand protein, rather than mutation that influence protein activity?**

**Tang**: Elevated sonic hedgehog, desert hedgehog, or Indian hedgehog ligand concentrations may occur through autocrine signaling (secretion by the tumor itself) or paracrine signaling (elevated ligand release from the stroma). This ligand-induced hedgehog pathway activation has been proposed as one mechanism by which the hedgehog signaling pathway might play a role in certain non-BCC, non-medulloblastoma cancers, such as subsets of gastrointestinal or breast cancer.
1. The most common basal cell carcinoma (BCC) subtype is:
   A. Superficial
   B. Nodular
   C. Morpheaform
   D. Basosquamous

2. Which of the following is characterized by multiple BCCs, palmoplantar pits, calcification of the falx cerebri, and bridging of the sell turcica?
   A. Nodular BCC
   B. Metastatic BCC
   C. Basal cell nevus syndrome
   D. Locally advanced BCC

3. Which of the following is an approved treatment alternative only for superficial BCC?
   A. Chemotherapy
   B. Combination therapy
   C. Cryosurgery
   D. Photodynamic therapy

4. Which of the following is TRUE regarding the incidence of metastatic BCC?
   A. Large-scale patient registries have provided highly reliable estimates of incidence and prevalence.
   B. Estimated incidence rates have varied from 0.0028% to 0.55%.
   C. Most studies that examined the incidence of metastatic BCC were conducted within the last 5 to 10 years.
   D. At least 3,000 cases of metastatic BCC have been reported in the medical literature.

5. Randomized controlled clinical trials have demonstrated the effectiveness of which chemotherapy strategy for the treatment of metastatic BCC?
   A. Platinum-based chemotherapy
   B. Gemcitabine
   C. Temozolomide
   D. None of the above

6. The transmembrane protein Smoothened (Smo) has an inherent tendency to:
   A. Absorb ultraviolet radiation
   B. Suppress DNA transcription
   C. Upregulate the secretion of epidermal growth factor receptor (EGFR)
   D. Activate a proliferative signal within cells

7. The binding of PTCH to its ligand, hedgehog protein:
   A. Inhibits Smo activity
   B. Releases repression of Smo
   C. Prevents BCC formation
   D. Stimulates production of cyclopamine

8. The hedgehog pathway inhibitor vismodegib is a new treatment option for patients with:
   A. Melanoma
   B. Multiple myeloma
   C. Metastatic breast cancer
   D. Advanced basal cell carcinoma

9. Locally advanced BCCs are NOT treated using:
   A. Surgical excision
   B. Micrographic surgery
   C. Topical therapy
   D. Radiation therapy

10. Once-daily oral vismodegib rapidly introduces what to existing BCCs?
    A. Shrinkage
    B. Infection
    C. Discoloration
    D. Inflammation
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