Translational Genomic Research and the Treatment of Basal Cell Carcinoma

Skin Cancers and Their Etiologies
Elucidating the Role of Molecular Signaling Pathways in the Tumorigenesis of Basal Cell Carcinoma
Assessing Current Treatment Options for Patients With Severe/Advanced Basal Cell Carcinoma
Emerging Treatments and Signaling Pathway Inhibitors

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Original Release Date: December 2011
Most Recent Review Date: December 2011
Expiration Date: December 2013
Estimated Time to Complete Activity: 2.0 hour(s)
Medium or Combination of Media Used: Written Supplement
Method of Physician Participation: Journal Supplement
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Reprinted from Seminars in Cutaneous Medicine and Surgery

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Acknowledgments

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LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Articulate the mechanisms of DNA damage associated with sporadic BCCs and the underlying causes of genetic mutations seen in BCCs in patients with Gorlin syndrome (also called basal cell nevus syndrome or nevoid basal cell carcinoma syndrome)
- Assess the risk for progression and recurrence associated with the clinical subtypes of BCC
- Explain the Hedgehog signaling pathway and its role in normal tissue development as well as in the tumorigenesis of BCC and other cancers
- Define advanced or severe BCC, describe the genetic mechanisms that have been identified, and explain how emerging targeted therapies may be used as chemoprevention in patients with Gorlin syndrome
- Describe the putative method of action of emerging agents that may be used as chemoprevention in the treatment of patients with advanced BCC
- Educate patients about treatment options and pharmacologic therapies that are currently available for advanced, refractory, or unresectable BCC
- Appropriately incorporate into clinical practice one or more of the targeted treatments that act on the Hedgehog pathway, as these agents become available.

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Method of Physician Participation: Journal Supplement

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This continuing medical education (CME) supplement was written from interviews with the Guest Editors. The manuscript was reviewed and approved by the Guest Editors as well as the Editors of Seminars in Cutaneous Medicine and Surgery. The ideas and opinions expressed in this supplement are those of the Guest Editors and do not necessarily reflect the views of the supporter or of the Publisher.

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Skin cancers are the most common form of malignancy. Early diagnosis and treatment provides the best chance for survival and reduced morbidity. However, some patients have recurrent or resistant lesions. In patients with basal cell carcinoma (BCC), prognosis is relatively good for all four types of lesions (superficial, nodular, infiltrative, and morpheaform), but the highest recurrence rates and greatest morbidity are associated with infiltrative and morpheaform BCC, and prognosis is least favorable when perineural invasion has occurred. Research into the etiology of BCC and other skin cancers has led to the identification of several genetic mutations—those of the Patched and Hedgehog genes. By targeting these pathways, treatments aimed at driver mutations hold promise for new nonsurgical treatments.

Semin Cutan Med Surg 30:S1-S5 © 2011 Elsevier Inc. All rights reserved.
Three main clinical subtypes of BCC are recognized; they are superficial, nodular, and sclerosing/morpheaform. Each of these variants can be pigmented or nonpigmented, and various types may occur simultaneously within the same tumor, and each can have an infiltrative component seen under histology (Figures 1-3). Most lesions occur on the head and neck, but an increasing number of BCCs are being diagnosed on the torso and even on anatomic sites protected from the sun.

Nodular BCC lesions usually are seen on the head and neck and appear as pearly, telangiectatic papules with rolled borders. Ulceration and crusting sometimes occurs. Superficial BCC appears as an erythematosus plaque, typically on the trunk or extremities. Morpheaform lesions often resemble scars and usually are the most difficult to identify on visual inspection alone, often lacking the pearly and telangiectatic characteristics seen in superficial and nodular BCCs; palpation of a morpheaform BCC usually reveals areas of subclinical extensions. Infiltrative basal cell tumors most commonly occur in association with nodular or morpheaform lesions. Furthermore, melanocytes can transfer melanin to basal cells or they can colonize basal cell tumor islands. If this occurs, the basal

Table 1 Basal Cell Carcinoma (BCC) Risk Factors11-16

<table>
<thead>
<tr>
<th><strong>Environmental Factors</strong></th>
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<tr>
<td>Ultraviolet radiation, especially</td>
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<tr>
<td>– Intermittent sun exposure</td>
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<tr>
<td>– Childhood sun exposure</td>
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<td>– Blistering sunburns</td>
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<td>Arsenic exposure</td>
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<tr>
<th><strong>Phenotypic Attributes</strong></th>
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<tr>
<td>Fair skin</td>
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<td>Blue eyes</td>
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<td>Blond or red hair</td>
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<tr>
<td>Advancing age*</td>
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<td>Male gender*</td>
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<th><strong>Individual Characteristics</strong></th>
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<tr>
<td>Previous BCC</td>
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<tr>
<td>Radiation therapy</td>
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<tr>
<td>Family history of skin cancer</td>
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<tr>
<td>History of nevoid basal cell carcinoma syndrome (Gorlin syndrome)</td>
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<tr>
<td>Immunosuppression</td>
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* A recent population-based study12 suggests that the incidence of nonmelanoma skin cancer may be increasing in younger adults (<40 years of age), including women.

Figure 1  Nodular Basal Cell Carcinoma.
Top: Nonpigmented nodular BCC: clinical photo (left) and dermoscopic image (right).
Bottom: Pigmented nodular BCC: clinical photo (left) and dermoscopic image (right).
Photos courtesy of Ashfaq A. Marghoob, MD.
scopic examination, then histopathologic examination of a specimen may be necessary. Experienced clinicians usually have little difficulty identifying lesions that raise suspicion of BCC based on the lesions morphology and anatomic site. However, a number of conditions are associated with lesions that may mimic BCC clinically; these are listed in Table 2.17 BCC can usually be distinguished from many of these other conditions by means of dermoscopy. However, if a conclusive diagnosis cannot be made on the basis of clinical and dermoscopic examination, then histopathologic examination of a biopsy specimen may be necessary.

BCCs associated with Gorlin syndrome also warrant a brief discussion here. Gorlin syndrome—also called basal cell nevus syndrome or nevoid basal cell carcinoma syndrome—is a condition transmitted in an autosomal dominant fashion that is characterized by multiple BCCs as well as skeletal anomalies and noncutaneous tumors, particularly medulloblastoma (the other tumors that have been described include ovarian and cardiac fibromas, meningioma, fibrosarcoma, and rhabdomyosarcoma). The BCCs in patients with Gorlin syndrome tend to occur on the central portion of the face, although they can occur at any anatomic site. The lesions often mimic nevi or skin tags, but they may present as any of the clinical BCC variants described.

With early diagnosis and appropriate treatment, the prognosis is relatively good for each type of BCC, although the highest recurrence rates and morbidity are associated with morpheaform BCC and with BCCs that have an infiltrative component. In addition, large lesions carry a poorer prognosis, and BCC with perineural invasion is associated with the least favorable outcome.

Anatomic location is another indicator of risk for progression and complications in BCC. Lesions that occur on the area referred to as the H of the face (perinasal and periauricular regions) also are associated with a greater risk for recurrence.

In most patients, the standard treatments currently available for BCC yield favorable outcomes with low rates of recurrence. However, in some cases, lack of early treatment or undertreatment results in the growth of tumors that are large or that have advanced contiguously into deeper tissue layers. In such cases, surgery can be associated with significant cosmetic disfigurement, such as the total or partial loss of the
It has been known for some time that the p53 gene plays a crucial role in cell division and also that UV radiation can damage the p53 gene. Simply put, p53 creates a transcription factor that allows a cell to identify errors in its DNA just before DNA replication is to occur. The transcription factor also enables the cell to either fix any replication errors it finds or (if the damage cannot be fixed) to stop the cell division process. The hazard associated with a failure of p53 to create this transcription factor is obvious: damaged DNA can be replicated, and mutant cells can go on to divide unchecked.

More recently, two other genes important to the BCC story have been identified: Patched and Hedgehog. To review an extremely complex topic very briefly, Patched is associated with normal cell growth and is directly involved in apoptosis. Within the last decade, investigators have determined that Patched is located on the ninth chromosome in human cells, and its malfunction or inactivation is associated with the development of cell anomalies, including BCC and other cancers. Hedgehog was identified as a gene that activates Patched; Hedgehog and Patched, working in a balanced way in tandem, play principal roles in healthy cell growth, development, and programmed death.

The importance of these discoveries relating to the mechanisms underlying the development of cancer cannot be overstated. Indeed, treatments that target cellular malfunction at the...
Table 2 Differential Diagnosis of Basal Cell Carcinoma (BCC) Lesions by Type17

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Differential Diagnosis</th>
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<tr>
<td>Nodular</td>
<td>Seborrheic keratosis, Trichoepithelioma, Sclerosing nevus</td>
</tr>
<tr>
<td>Superficial</td>
<td>Eczema, Bowen disease, Psoriasis, Tinea corporis</td>
</tr>
<tr>
<td>Morpheaform</td>
<td>Morphea (localized scleroderma), Lichen sclerosis et atrophicans, Scar</td>
</tr>
<tr>
<td>Pigmented</td>
<td>Blue nevus, Angiokeratoma, Hemangioma, Seborrheic keratosis, Melanoma</td>
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BCC can be readily distinguished from most of these conditions via the use of dermoscopy. If the diagnosis cannot be confirmed on the basis of clinical and dermoscopic examination, then histopathologic examination may be necessary.

Nodular
- Intradermal nevus
- Sebaceous hyperplasia
- Squamous cell carcinoma
- Dermatofibroma
- Epidermal inclusion cyst
- Furuncle
- Hemangioma
- Seborrheic keratosis
- Neurofibroma
- Follicular tumors
- Trichoblastoma
- Trichofolliculoma
- Trichoepithelioma
- Sclerosing nevus

Superficial
- Eczema
- Bowen disease
- Psoriasis
- Tinea corporis

Morpheaform
- Morphea (localized scleroderma)
- Lichen sclerosis et atrophicans
- Scar

Pigmented
- Blue nevus
- Angiokeratoma
- Hemangioma
- Seborrheic keratosis
- Melanoma

References

most basic level have been used for a number of years. One of these is imiquimod, which was the first topical immune response modifier developed and marketed in the United States. Originally approved for the treatment of genital warts, imiquimod’s benefit in the treatment of superficial BCC was subsequently investigated and recognized, even prior to the clear elucidation of the drug’s mechanism of action in BCC.

Earlier in 2011, a targeted therapy for melanoma was introduced in the United States, and, currently, work continues on a number of other driver mutation treatments. In the realm of BCC, the most promising agents at present are Smoothened pathway inhibitors, which target the Hedgehog pathway.

Conclusion

BCC is associated with significant morbidity, even in patients who do not experience significant spread or recurrence of lesions. Individuals who have more significant involve-
The first line of defense against skin cancer is primary prevention. Of the three recognized environmental causes for basal cell carcinoma (BCC)—ultraviolet (UV) radiation, ionizing radiation, and arsenic—UV is the most important preventable cause of BCC. UV exposure from either the sun or tanning beds has been associated with p53 gene mutations and squamous cell carcinoma. In BCC, mutations in tumor suppressor genes have been identified as the underlying mechanism of tumorigenesis, possibly resulting from intermittent exposures (such as childhood episodes of sunburn or weekend sunbathing).

Once cells have sustained DNA damage, however, attention necessarily shifts to secondary prevention and, if secondary prevention fails, to treatment. Research focusing on the molecular pathogenesis in BCC has yielded crucial findings that have implications for both secondary prevention and treatment. A major advance was the identification of the Hedgehog signaling pathway.

**What Is the Hedgehog Signaling Pathway?**

The Hedgehog signaling pathway is a developmental pathway that was originally identified during embryonic research on the fruit fly, *Drosophila melanogaster*. In that endeavor, investigators identified the Hedgehog ligand, its transmembrane receptor known as Patched, and a number of down-
stream components of the Hedgehog signal transduction pathway. Subsequent studies showed that the Hedgehog pathway was critical to the proper formation of segments in embryonic *Drosophila*, determining the basic body structure: the anterior-posterior relationships of structures (“segment polarity”).

The Hedgehog signaling pathway is a well-conserved developmental pathway from insects through mammals, with mammals retaining homologs for a number of Hedgehog components. Three homologs have been identified in humans, including the Sonic Hedgehog homolog (Shh), which is known to be important for the embryonic development and maintenance of the nervous system, axial skeleton, lungs, skin, hair, and stem cells. Shh is secreted by—and binds to—its receptor, Patched 1. Patched 1 is crucial to the regulation of the Hedgehog signaling pathway, an important finding that bears on the understanding of BCC development.

The mechanism by which Patched 1 inhibits Shh signaling is complex (Figure). Patched 1 represses the activity of a receptor called Smoothened, which normally activates a family of transcription factors, termed glioma-associated transcription factors (Gli1, Gli2, and Gli3). These three transcription factors control the expression of Patched 1 (which provides a negative feedback of Hedgehog signaling) and of Gli1 itself (which provides a positive feedback of Hedgehog signaling). Hedgehog-binding proteins (including Hedgehog-interacting protein [Hip]) sequester the Hedgehog ligand and thus regulate how much Shh is available to bind Patched 1.

Further work is needed to more fully define the signaling downstream of the Smoothened receptor, but Kogerman and colleagues have reported that a protein called suppressor-of-fused (Sufu) binds to Gli and prevents activation of the Hedgehog target genes, and numerous other investigators (including Incardona and Roelink and Ingham and McMahon) have further defined the signaling events involving Shh, Patched 1, Smoothened, and Gli in normal cells.

### The Hedgehog Signaling Pathway in BCC Tumorigenesis

Postembryonic activity of the Hedgehog signaling pathway is normal only in hair follicles and skin cells, in which this signaling pathway drives their maintenance; in all other cells except stem cells, the pathway is no longer active.

As Quinn and Epstein found almost a decade ago, an overactive Shh signaling pathway is extremely common in BCC tumors, and the most common cause of this overactivity is inactivation of Patched 1, resulting from mutations in Patched 1. (This recognition led to the observation that Patched 1 is a potential tumor suppressor gene.)

Gorlin syndrome, a commonly used eponym for basal cell nevus syndrome or nevoid basal cell carcinoma syndrome, is a rare, autosomal dominant genetic condition. In 1992, Farkdon and colleagues in the United Kingdom estimated a prevalence of 1 in 57,000, but other epidemiologic studies have suggested that the prevalence may vary widely among populations. For example, in Australia, Shanley and colleagues noted a much lower estimated prevalence of 1 in 164,000, Lo Muzio and coworkers reported an even lower prevalence in Italy of 1 in 256,000, and, more recently, Ahn...
and colleagues in Korea reported a prevalence of 1 in almost 24 million individuals.

Gorlin syndrome is characterized by multiple neoplasms and by any of a number of developmental abnormalities. The developmental abnormalities include palmar and/or plantar pits, falk cerebri calcification, coarse facies with frontal bossing, cleft lip and/or palate, spina bifida occulta, bifid ribs, macrocephaly, polydactyly, and eye anomalies (such as strabismus). In addition to BCC, the benign and malignant neoplasms associated with Gorlin syndrome include odontogenic keratocysts, medulloblastomas, meningiomas, rhabdomyosarcomas, fibrosarcomas, and ovarian and cardiac fibromas.

Pathways to Secondary Prevention and Treatment

Almost invariably, BCCs in individuals with Gorlin syndrome are caused by a mutation of the Patched 1 gene. This feature shared by most BCCs that arise sporadically in individuals without Gorlin syndrome, in whom the mutation is the result of environmental insult, as described above. This Hedgehog signaling abnormality also has been noted in BCCs that occur in patients with xeroderma pigmentosum. Most BCCs result from loss of function mutations in Patched 1, and a minority of BCCs result from gain of function mutations in Smoothened. In both cases, Smoothened is activated.

For the vast majority of patients, BCCs are sporadic, few in number, and relatively small (provided these tumors are diagnosed early and treated successfully). In these cases, several treatment options are available, including surgical modalities—Mohs micrographic surgery, in particular—and nonsurgical therapy (for carefully selected cases of superficial BCCs). Unfortunately, current treatments are not fully effective for a limited number of patients: those with advanced disease, individuals with large tumors that are either inoperable or located in anatomic areas in which surgery is considered to be high-risk, or patients with Gorlin syndrome, who may have dozens to many hundreds of tumors over a lifetime. For these individuals, blocking the Hedgehog pathway is a strategy that offers hope.

One strategy that is proving beneficial, both in animal models and clinical trials, is the development of small-molecule agents that bind to Smoothened and thus turn off the Hedgehog pathway. Chen and Beachy found the first Smoothened inhibitor, cyclopamine, a steroid alkaloid derived from the California corn lily plant. Chen and colleagues determined that cyclopamine binds to Smoothened and blocks activation of Hedgehog target genes downstream. Subsequently, other Smoothened inhibitors were identified that offer higher-potency and more-selective activity than cyclopamine.

In 2009, Rudin and colleagues showed that one such molecule, GDC-0449, was effective in treating medulloblastomas in a murine model. A phase I clinical trial evaluated the safety and adverse event profile of daily administration of an oral formulation of GDC-0449 in patients with metastatic or locally advanced BCC and other solid tumors. The 33 patients in the study took the drug for a median of 9.8 months; 18 patients showed either a complete (2 patients) or a partial (16 patients) response on imaging, physical examination, or both. The rest of the patients had either stable (11) or progressive (4) disease. Only 1 patient dropped out of the study because of adverse effects.

A multinational, single-arm, two-cohort, open-label phase II study of vismodegib (previously known as GDC-0449), called ERIVANCE BCC, was completed in 2011. The results were submitted to the US Food and Drug Administration in September 2011 as part of a new drug application. The ERIVANCE BCC study involved 104 patients with advanced BCC—locally advanced and/or metastatic BCC—who were not considered to be appropriate candidates for surgery. Among the patients with locally advanced BCC, 43% experienced substantial shrinkage of tumors or healed visible lesions; 30% of patients experienced metastatic BCC tumor shrinkage. The most common adverse events were muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea. Deaths did occur during the study and are being further evaluated; to date, these do not appear to be related to the study drug.

An investigator-initiated, phase II, randomized, placebo-controlled trial of vismodegib was conducted in 41 patients with Gorlin syndrome from September 2009 to January 2011. The primary end point of the study was the number of new surgically eligible BCCs after 3 months of treatment with either vismodegib (at a daily oral dosage of 150 mg) or placebo. The secondary end points were safety, tolerability, and a change in the size of existing BCC tumors.

The placebo arm of the trial was ended early, at the point of interim data analysis, because statistically significant differences were observed between the vismodegib and placebo groups. Prior to the interim analysis, 24 patients who had received GDC-0449 had 0.07 new BCCs per month, vs 1.74 BCCs per month observed in patients in the placebo group ($P<0.001$). In addition, existing BCCs decreased by 24 cm in the patients treated with GDC-0449 and by 3 cm in the control group ($P=0.006$).

Other studies of GDC-0449 are under way, as are studies of other Hedgehog pathway inhibitors, including, in particular, Smoothened inhibitors.

Conclusion

The early work done to elucidate the developmental mechanisms involved in the formation of Drosophila melanogaster has yielded important evidence regarding molecular signaling pathways. The most important of these, with regard to human disease, is the discovery and elucidation of mechanisms involved in the Hedgehog signaling pathway. To date, this information has been crucial to the understanding of BCC, in particular, and has led to the subsequent development of potential treatments for this malignancy. Smoothened inhibitors hold the most immediate promise for treating patients—such as those with locally invasive or metastatic BCC—who are not candidates for surgery.

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Assessing Current Treatment Options for Patients With Severe/Advanced Basal Cell Carcinoma

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Professor of Dermatology and Community Health, Alpert Medical School, Brown University
Providence, Rhode Island

Skin cancers are the most common form of malignancy, and basal cell carcinoma (BCC) is the most common form of skin cancer. BCCs generally occur sporadically and either singly or in small numbers. When detected and treated early, these tumors are highly curable. When therapy is chosen that is appropriate to the subtype and anatomic location of the lesion, the recurrence rate typically is low. Tumors that are recurrent, aggressive, unresectable, advanced, and/or metastatic are more difficult to treat successfully, as are the multiple BCCs that occur commonly in patients with the genodermatosis known as Gorlin syndrome (also called basal cell nevus syndrome or nevoid basal cell carcinoma syndrome). For these difficult-to-manage patients, the hope for the future lies in chemoprevention.

Semin Cutan Med Surg 30:S10-S13 © 2011 Published by Elsevier Inc.

Most basal cell carcinoma (BCC) tumors that are detected and treated early are readily cured with any of several destructive or excisional modalities. Because BCCs almost always spread contiguously (rather than by metastasis), recurrence typically is not a problem unless the margins of treatment are insufficient. When BCC progresses untreated or undertreated (as, for example, when surgical excision of facial tumors is less extensive than necessary because of cosmetic concerns), tumors can enlarge substantially and/or involve deeper skin layers, underlying tissue, or even bone. Such cases may be referred to as “advanced” or “severe” BCC, although no specific definitions of those two terms are widely accepted.

A variety of modalities currently are used to treat BCCs. Choosing the most effective treatment—that is, the one single modality or the combination of modalities that is most likely to be curative—depends on several factors, including an assessment of risk. According to the National Comprehensive Cancer Network (NCCN), the initial treatment for tumors that arise in non–hair-bearing sites is either standard excision or curettage and electrodesiccation (C&E). However, when any of nine risk factors (Table 1) is present, Mohs surgery may be recommended—with or without the concomitant use of other modalities. (Note that guidelines from NCCN are updated as needed, based on continual review of the latest published literature by a panel of experts. Clinicians can access the latest guidelines online, at www.nccn.org/professionals/physician_gls/f_guidelines.asp.) The specific treatment pathway depends on both patient characteristics and the BCC tumor subtype; Cockerell and colleagues summarized their recommendations (Table 2).

In the following sections, some observations regarding important risks and benefits associated with various treatment modalities are highlighted. However, this is not intended to be a comprehensive discussion of BCC treatment; so many variables must be considered in the choice of treatment for individual patients—and, in fact, for individual BCCs that...
Table 1 Risk Factors for Recurrence of Basal Cell Carcinoma

<table>
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<th>Risk Factor</th>
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<td>Diameter is &gt;20 mm on trunk and extremities</td>
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<td>Diameter is &gt;10 mm on cheeks, forehead, scalp, or neck</td>
<td></td>
</tr>
<tr>
<td>Diameter is &gt;6 mm on genitalia, hands, feet, or face (except cheeks and forehead)</td>
<td></td>
</tr>
<tr>
<td>Tumor borders are poorly defined</td>
<td></td>
</tr>
<tr>
<td>Tumor is recurrent</td>
<td></td>
</tr>
<tr>
<td>Patient is immunosuppressed</td>
<td></td>
</tr>
<tr>
<td>Tumor arises in area of prior radiation therapy</td>
<td></td>
</tr>
<tr>
<td>Tumor has any evidence of morpheaform, sclerosing, mixed infiltrative, or micronodular histologic features</td>
<td></td>
</tr>
<tr>
<td>Tumor involves perineural region</td>
<td></td>
</tr>
</tbody>
</table>

Source: National Comprehensive Cancer Network.

Basal cell carcinoma tumors are at risk for recurrence if any of the following factors are present:

- Diameter is >20 mm on trunk and extremities
- Diameter is >10 mm on cheeks, forehead, scalp, or neck
- Diameter is >6 mm on genitalia, hands, feet, or face (except cheeks and forehead)
- Tumor borders are poorly defined
- Tumor is recurrent
- Patient is immunosuppressed
- Tumor arises in area of prior radiation therapy
- Tumor has any evidence of morpheaform, sclerosing, mixed infiltrative, or micronodular histologic features
- Tumor involves perineural region

Treatment Options for Low-Risk Tumors

In their seminal article on the treatment of BCC, Spiller and Spiller observed that C&E is curative in up to 98% of appropriately selected cases, but also noted that C&E should be repeated until the surgeon encounters a healthy base. For low-risk tumors—that is, those not associated with any of the nine risk factors for recurrence identified by the NCCN—C&E offers a readily available treatment, with greater convenience, and at a much lower cost than is associated with Mohs surgery. The disadvantages are that no tumor margins are identified and healing may be prolonged.

Standard surgical excision offers the advantages over C&E of margin control and, usually, better cosmetic results, but is more expensive and time-consuming than C&E and requires more skill and training to perform. Typically, the recommended excision margin for small, primary BCCs ranges from 3 to 5 mm, although a recent meta-analysis by Gullette and coworkers concluded that a surgical margin of 3 mm is safe and is associated with a 95% cure rate for nonmorpheaform BCCs that are ≤2 cm.

Treatment Options for Higher-Risk BCCs

As stated above, Mohs micrographic surgery often is the primary treatment of choice for BCCs associated with any of the nine risk factors for recurrence. It is the only technique that allows for complete histologic evaluation of the margins. It is the method that provides the best chance of complete removal of a BCC, while maximizing preservation of normal tissue.

For patients who are not good candidates for surgery, cryosurgery or radiation may be considered. Each has advantages and disadvantages in specific circumstances. For example, cryosurgery is low cost and may be particularly suitable when patients have many small lesions (especially when these are superficial or nodular and arise in low-risk anatomic sites). Radiation is an especially useful modality for BCCs in elderly patients.

Photodynamic therapy with aminolevulinic acid (PDT-ALA) has been used for superficial and nodular BCC, with widely varying results. In one review, published in 2007, the authors summarized the results of six studies, noting reported response rates from 79% to 100%, and recurrence rates ranging from 1% to 38%. It is important to note that the results of these studies are not directly comparable because of a wide variation in the number of subjects as well as methodologies, but for most BCCs and for otherwise-healthy individuals, other modalities are preferable, even for low-risk BCCs, when consistent effectiveness, cost, convenience, and availability of treatment are also weighed.

Topical imiquimod and 5-fluorouracil (5-FU) both are approved by the US Food and Drug Administration for the treatment of superficial BCCs in certain circumstances. These agents currently offer alternatives to surgery, but are associated with lower cure rates.

Gorlin Syndrome

For patients with Gorlin syndrome, in whom multiple lesions must be treated, a field therapy such as the topical agents 5-FU or imiquimod provide a welcome alternative to multiple surgeries. These agents can be helpful in eradicating tumors and, as a result, are potentially useful as chemopreventive agents in patients with Gorlin syndrome.

Recurrent, Unresectable, Advanced, and Metastatic BCC

Recurrence of a previously treated BCC results when malignant cells remain after treatment. Recurrence is least likely to occur following Mohs surgery, and it is most likely to occur in so-called high-risk anatomic areas: the embryonic fusion planes, as well as the scalp, eyelids, temples, ears, nose, and lips.

Currently, unresectable and advanced disease usually is treated with a combination of cisplatin and doxorubicin chemotherapy, plus radiation. In patients in whom metastasis has occurred to the regional nodes, surgical removal of the nodes is necessary, possibly combined with radiation. In the rare case of systemic metastatic disease, cisplatin/doxorubicin is the systemic therapy of choice, combined with radiation, when necessary.

Conclusion

In most patients who develop BCC, early detection and treatment yields a satisfactory outcome. Individual patient characteristics, tumor subtype, and other factors including cost must be considered in selecting the most appropriate destructive or excisional treatment. Recurrence usually is only a problem when the margins of treatment are not sufficient.

Untreated or undertreated BCC can progress contiguously, in terms of both surface spread and tissue depth, even including bone tissue. Rarely, BCCs can metastasize. Patients with Gorlin syndrome may benefit from chemopreventive agents such as 5-fluorouracil or imiquimod.
<table>
<thead>
<tr>
<th>Type of BCC</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular &lt;2 cm (trunk, extremities)</td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td>Curettage and electrodesiccation (lesions should not be deeply invasive)</td>
</tr>
<tr>
<td></td>
<td>Cryosurgery ± curettage</td>
</tr>
<tr>
<td></td>
<td>Radiation*</td>
</tr>
<tr>
<td></td>
<td>Note: for lesions &gt;2 cm, Mohs surgery is preferred</td>
</tr>
<tr>
<td>Nodular &lt;1 cm (cheeks, forehead, scalp, or neck)</td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td>Curettage and electrodesiccation (lesions should not be deeply invasive)</td>
</tr>
<tr>
<td></td>
<td>Cryosurgery ± curettage (skillful clinicians only)</td>
</tr>
<tr>
<td></td>
<td>Radiation*</td>
</tr>
<tr>
<td></td>
<td>Note: for lesions &gt;1 cm, Mohs surgery is preferred</td>
</tr>
<tr>
<td>Nodular &lt;0.6 cm (face except cheeks or forehead, genitalia, hands or feet)</td>
<td>Excision; Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Cryosurgery ± curettage (skillful clinicians only—may want pre- and post-treatment biopsies)</td>
</tr>
<tr>
<td></td>
<td>Radiation (may want pre- and post-treatment biopsies)*</td>
</tr>
<tr>
<td></td>
<td>Note: for lesions &gt;0.6 cm, Mohs surgery is preferred</td>
</tr>
<tr>
<td>Superficial (multicentric)</td>
<td>Shave excision with curettage ± electrodesiccation</td>
</tr>
<tr>
<td></td>
<td>Curettage and electrodesiccation</td>
</tr>
<tr>
<td></td>
<td>5% imiquimod</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil (may need to use with curettage or occlusion)</td>
</tr>
<tr>
<td></td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td></td>
<td>Cryosurgery</td>
</tr>
<tr>
<td></td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td>Mohs surgery (if recurrent or large, eg &gt;2 cm)</td>
</tr>
<tr>
<td></td>
<td>Radiation (extremely superficial X-ray required; not a usual or preferred method)*</td>
</tr>
<tr>
<td>Morpheaform</td>
<td>Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Excision (if Mohs surgery not available)</td>
</tr>
<tr>
<td>Aggressive growth pattern</td>
<td>Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Excision (if Mohs surgery not available)</td>
</tr>
<tr>
<td></td>
<td>Radiation (may require pre- and post-treatment biopsies)*</td>
</tr>
<tr>
<td>“Field fire”‡</td>
<td>Mohs surgery (allow wound to heal on its own if possible)†</td>
</tr>
<tr>
<td></td>
<td>Excision</td>
</tr>
<tr>
<td></td>
<td>Note: cryosurgery or radiation is not ideal, especially if possibly recurrent BCC</td>
</tr>
<tr>
<td>Metatypical</td>
<td>Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Excision (if Mohs surgery not available)</td>
</tr>
<tr>
<td></td>
<td>Radiation (may need pre- and post-treatment biopsies)*</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Excision (if Mohs surgery not available)</td>
</tr>
<tr>
<td>Neurotropic</td>
<td>Mohs surgery†</td>
</tr>
<tr>
<td></td>
<td>Excision (if Mohs surgery not available)</td>
</tr>
<tr>
<td></td>
<td>Some of these patients may require postoperative radiation</td>
</tr>
<tr>
<td>Incompletely excised</td>
<td>Re-excite in conventional manner or by Mohs surgery</td>
</tr>
<tr>
<td>Unresectable and advanced disease</td>
<td>Cisplatin + doxorubicin + radiation</td>
</tr>
<tr>
<td>Metastases to regional nodes</td>
<td>Surgical removal of the nodes; may need to combine with radiation</td>
</tr>
<tr>
<td>Systemic metastases</td>
<td>Cisplatin + doxorubicin; may use with radiation when necessary</td>
</tr>
</tbody>
</table>

Source: Reprinted with permission from Cockerell CJ et al. *Should not be used in younger patients. †Preferred treatment. ‡A BCC variant that may be seen in a previously irradiated field or a multifocal recurrent BCC. The margins may be difficult to determine clinically.
syndrome experience many BCCs (sometimes many hundreds) over a lifetime. In patients with this genodermatosis, or in those with advanced contiguous tumors or metastasis, Mohs micrographic surgery—with or without adjunctive therapy—currently is the standard of care. Chemoprevention strategies, many of which involve targeted molecular treatments already in clinical trials, show promise for preventing BCC tumors from occurring in patients with a genetic predisposition to this disease and in those in whom DNA damage already has occurred, and, possibly, for debulking or clearing BCCs.

References


References continued from page 10


Elucidating the Role of Molecular Signaling Pathways in the Tumorigenesis of Basal Cell Carcinoma

References

B

asal cell carcinoma (BCC) is the most common malig
nancy in humans, accounting for about 25% of all can
cers in the United States.1 Most nonmelanoma skin cancers
(NMSCs)—both BCC and squamous cell carcinoma
(SCC)—are caused by ultraviolet (UV) light damage to DNA
(most commonly from sun exposure, but UV damage from
tanning beds has become increasingly common). For this
reason, effective primary prevention strategies constitute the
first line of defense.

When primary prevention fails, BCC is, in most cases, a
treatable malignancy; the currently available treatment op-
tions are associated with high rates of success, when chosen
appropriately and applied skillfully. For example, BCCs that
are superficial and at low risk for progression (based on the
National Comprehensive Cancer Network guidelines)2 may
be treated with the topical immune modulator imiquimod,
radiation by chemical destruction (with 5-fluorouracil [5-FU] or
photodynamic therapy with aminolevulinic acid [PDT-ALA]),
by mechanical destruction (curettage and electrodesiccation or
cryosurgery), or radiation by surgical excision. BCCs at higher
risk for progression (nodular, infiltrative subtypes) may be
more appropriately treated with surgical excision or by Mohs
micrographic surgery, with or without adjunctive modalities.

However, in a small number of patients (less than 1% of
the population in the United States3), BCCs progress—that
is, they metastasize, or they advance locally to a depth, size,
or extent that makes them completely unresectable or ex-
tremely difficult to excise. In addition, excision is problem-
atic for another small group of patients: those with basal cell
nevoid syndrome, also referred to as nevoid basal cell carci-
noma syndrome or Gorlin syndrome. Patients with this au-
tosomal dominant genetic disorder may develop up to many
hundreds of BCC tumors over a lifetime.

Secondary Prevention of BCC

Secondary prevention of BCC—that is, prevention of pro-
gression to malignancy once DNA photodamage already has
occurred (or, in the case of Gorlin syndrome, the DNA mu-
tation has been inherited)—has been the topic of numerous

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Emerging Treatments and Signaling Pathway Inhibitors

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A number of therapies that target components of the Hedgehog signaling pathway currently
are in clinical trials. The specific molecules that seem most promising in basal cell
carcinoma and a number of other cancers are those that target the Smoothened transmem-
brane protein. The pivotal phase II trials have been completed on the Smoothened inhibitor
known as GDC-0449; five other agents (BMS-833923, LDE225, LEQ506, IPI926, and
TAK-441) have also shown promise in animal studies and early clinical trials and have
shown some efficacy in a variety of cancers that are affected by the Hedgehog signaling
pathway.

Semin Cutan Med Surg 30:S14-S18 © 2011 Elsevier Inc. All rights reserved.
lines of research over the past 4 decades. As Demierre and Krathen have summarized, investigators have explored and continue to explore strategies to (1) repair DNA photodamage, (2) remove damaged (premalignant) cells, (3) prevent additional mutations from occurring, (4) inhibit the consequential effects of oncogenic activity, and (5) reactivate non-functional tumor suppressor genes. The agents that are candidates for accomplishing these functions include drugs that currently are available (eg, systemic and topical retinoids, imiquimod, 5-FU, and PDT), several investigational drugs that are now being tested in clinical trials, some that are in earlier stages of development, and many that are still theoretical, described only in terms of their possible mechanisms of action (Table 1).

### Retinoids

Systemic and topical retinoids both have been investigated in BCC tumors in patients with Gorlin syndrome and in those with xeroderma pigmentosum and in patients with other conditions that put them at high risk for developing NMSCs.

Vitamin A and derivatives of retinol have been shown to be important in the maturation and differentiation of epithelial cells, but the exact mechanism of action remains unknown. Several mechanisms have been proposed and are being explored, including an influence on growth factors, an indirect effect on processes involved in the downregulation of proto-oncogenes, and an increase of ceramide levels within the cells—any or all of which could result in decreased cell growth and slow or halt progression to malignancy.

In clinical studies, these agents have demonstrated efficacy in secondary prevention, but the benefits persist only as long as the drugs are used. Aside from the risk for teratogenicity—which is associated with short- as well as long-term use—the long-term use of systemic retinoids is associated with an increased risk for side effects that preclude lifelong treatment.

Topical retinoid therapy is another treatment that may be helpful in secondary prevention. However, preliminary data from the Veterans Affairs Topical Tretinoin Chemoprevention Trial have not demonstrated significant benefit of this agent for chemoprevention.

### Topical field therapy

Imiquimod, 5-FU, and PDT–ALA or PDT with methyl aminolevulinate (PDT–MAL) are categorized as field therapy, although the mechanisms of action among these agents differ. Imiquimod works on Toll-like receptors, enhancing host immunity and thereby triggering tumor cell destruction. In clinical studies, imiquimod 5% cream was effective for treating superficial BCCs, but was less effective for nodular BCCs. In a small, open-label series published by Huber and colleagues in 2004, 15 patients with nodular BCCs had 100% clearance of their lesions. A more recent study by Eigentler and colleagues showed that imiquimod treatment resulted in histologically confirmed clearance in about 50% of the low-risk nodular BCCs in their series of 102 patients. However, 36% of patients had persistent tumors at the end of the study.

A large, double-blind, randomized, vehicle-controlled chemoprevention trial of topical 5-FU currently is under way in the Veterans Affairs (VA) medical system. Officially titled the CSP #562–VA Keratinocyte Carcinoma Chemoprevention Trial, about 12 VA centers and approximately 1,000 patients will be involved. The subjects will be veterans who are at high risk for developing skin cancer; in this study, high risk is defined as the diagnosis of two keratinocyte carcinomas (ie, BCC or SCC) within the past 5 years, at least one of which was located on the face or ears. 5-FU is thought to selectively destroy premalignant cell clones.

PDT—PDT–ALA or PDT–MAL—also may work by selective destruction of premalignant clones. In addition, however, there is some evidence that upregulation of a host-response or cellular-mediated immunity may contribute to the delay in progression to BCC and SCC that is seen following PDT treatment.

### T4 endonuclease V

The bacterial DNA repair enzyme, identified as T4 endonuclease V, also has been shown to enhance repair of human DNA in laboratory experiments in which it is delivered into the cell. In animal studies, particularly in murine models, a number of studies have demonstrated the protective effects of topically applied T4 endonuclease V that has been encapsulated in liposomes; the experiments have involved the application of the encapsulated enzyme both before and after UVB exposure.

This strategy also has been tested in human subjects, in a randomized, double-blind, controlled trial of 30 patients with xeroderma pigmentosum. The patients in the active treatment group had a reduced rate of development of both BCCs and actinic keratoses compared to those in the control group. These promising results suggest that further study in this area is warranted.

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**Table 1 Interventions in Prevention After DNA Damage**

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Retinoids (oral and topical)</th>
<th>Imiquimod</th>
<th>Photodynamic therapy; topical 5-fluorouracil</th>
<th>T4 endonuclease V</th>
<th>Inhibitors of Hedgehog signaling pathway</th>
<th>No interventions established as effective to date</th>
</tr>
</thead>
</table>

**Source:** Reprinted with permission from Demierre & Krathen.
Hedgehog Signaling Inhibitor Strategy

Research on the genetics of development in the *Drosophila melanogaster* fruit fly, beginning in the 1970s, led to widespread investigations into how embryonic cells were “directed” to differentiate into specific structures at specific locations (for example, anterior vs posterior) to create the mature insect. Perhaps as interesting as the lines of research leading to the understanding of the normal pathways of development were the efforts to understand the mechanisms of development of mutant insects. From these and subsequent studies, much has been learned about the Hedgehog gene and about the components of the signaling pathway named for this ligand.

Investigators have determined that homologs of the components of the Hedgehog signaling pathway are well conserved through the species, and three homologs have been identified so far in humans. The best characterized is the Sonic Hedgehog homolog (Shh), which binds to, the receptor called Patched 1. Shh is known to have an important role in the development and maintenance of structures, including the nervous system, axial skeleton, lungs, skin, hair, and stem cells. Postdevelopmentally, the Hedgehog signaling pathway is inactive in all normal cells, with the exception of hair, skin, and stem cells.

Patch 1 has been identified as being key to the regulation of the Hedgehog signaling pathway, as loss-of-function (lof) mutations in Patched 1 leads to de-repression of Smoothened. The activated Smoothened then allows Gli to enter into the nucleus and activate genes responsible for cell growth. In genetically engineered mice, lof mutations in Patched, gain-of-function mutations in Smo, and overexpression of Gli all lead to BCC development. Activation of the Hedgehog pathway also has been implicated in the development of other forms of cancer, including, in particular, medulloblastoma; medulloblastoma, along with BCC, is a malignancy commonly found in patients with Gorlin syndrome.

With this body of research as a foundation, investigators theorized that controlling the Hedgehog signaling pathway would result in control of disease activity associated with abnormal Hedgehog function. In recent years, the best-characterized disease process related to abnormal function in the Hedgehog signaling pathway has been BCC. Most sporadic BCCs have mutations (usually UV-induced) in the Hedgehog signaling pathway. BCCs in Gorlin syndrome almost always have Patched 1 gene mutations. This same abnormality also has been seen in BCCs in individuals with xeroderma pigmentosum. Most BCCs have loss-of-function mutations in Patched 1 and a minority of BCCs have gain-of-function mutations in Smoothened.

Identification of the Hedgehog ligand, as well as Patched (the Hedgehog transmembrane receptor) and a number of components of the Hedgehog signal transduction pathway, led to the development of a roster of potential inhibitors of this pathway. Inhibition of key components of the Hedgehog pathway is now understood to be a way of controlling tumorigenesis in BCC and, possibly, a number of other types of cancer as well.

Smoothenened Inhibitors

The discovery of cyclopamine, an endogenous steroidal plant alkaloid, as an inhibitor of Smo ignited the quest for the identification of other agents that could inhibit the HH pathway. Cyclopamine binds to Smoothenened and inhibits downstream target genes. Subsequent studies led to the development of synthetic cyclopamine, as well as other molecules that target specific components in the Hedgehog signaling pathway.

One of the first such molecules to be developed is GDC-0449, which was tested in a murine model and was shown to be effective in treating medulloblastoma. Since then, other laboratory studies and early clinical trials demonstrated that an oral formulation of this agent was effective in treating metastatic or locally advanced BCC and other solid tumors.

In a phase I study, Von Hoff and colleagues tested GDC-0449 in 33 patients, 18 of whom had either a complete (2/33 patients) or partial (16/33) response; the disease remained stable in 11 other patients and progressed in 4 patients. An open-label phase II pivotal study (ERIVANCE BCC) of 104 patients with locally advanced and/or metastatic BCC was completed recently. Substantial tumor shrinkage or healed visible lesions were seen in 43% of subjects with locally advanced BCC and in 30% of patients with metastatic BCC (vismodegib formerly called GDC-0449).

Another study, an investigator-initiated, phase II controlled trial of GDC-0449 was conducted to determine this agent’s efficacy in preventing BCCs in patients with Gorlin syndrome. From September 2009 to January 2011, 41 patients with Gorlin syndrome were enrolled in the trial at one of three clinical centers and were randomized in a 2:1 ratio to receive either GDC-0449, orally, at a dosage of 150 mg/day or placebo. The primary end point was the number of new surgically eligible BCCs per month after 3 months. The secondary end points were a change in the size of existing BCC tumors as well as safety and tolerability.

The Data Safety Monitoring Board ended the placebo arm of the trial early because of statistically significant differences that were seen between the active treatment and placebo groups at the interim analysis of data. To that point, the 24 subjects who had been treated with GDC-0449 developed 0.07 new BCCs per month compared to 1.74 BCCs per month seen in patients in the placebo group (*P*<0.001). In the GDC-0449 group, the aggregate size of existing BCCs decreased by 24 cm; the decrease in aggregate size of BCCs in the placebo group was 3 cm (*P* = 0.006). Near-complete regression was seen in some patients in the treatment arm; no BCC lesion developed resistance.

The most common side effects seen in the GDC-0449 group were taste loss (83%, vs 8% in the placebo group), muscle cramps (67% vs 8%), and weight loss (50% vs 8%). Histologic clearance was seen in seven out of eleven lesion biopsies taken after 3 months of GDC-0449 therapy.
<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Condition(s) Studied</th>
<th>Additional Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDC-0449</td>
<td>Gorlin syndrome</td>
<td>Efficacy and safety study</td>
</tr>
<tr>
<td>GDC-0449</td>
<td>Advanced BCC</td>
<td>Efficacy and safety</td>
</tr>
<tr>
<td>GDC-0449</td>
<td>Locally advanced or metastatic solid tumors</td>
<td>Study in patients with tumors refractory to standard therapy or for whom no standard therapy exists</td>
</tr>
<tr>
<td>GDC-0449</td>
<td>Brain and CNS tumors</td>
<td>Study involves adult patients with recurrent or refractory medulloblastomas</td>
</tr>
<tr>
<td>GDC-0449</td>
<td>Brain and CNS tumors</td>
<td>Study in young patients with medulloblastoma, either recurrent or unresponsive to previous treatment</td>
</tr>
<tr>
<td>GDC-0449; biomarker analysis</td>
<td>Brain and CNS tumors</td>
<td>Study in younger patients with medulloblastoma, either recurrent or unresponsive to previous treatment</td>
</tr>
<tr>
<td>GDC-0449; bevacizumab; FOLFIRI regimen; FOLFOX regimen</td>
<td>BCC; metastatic colorectal cancer; ovarian cancer</td>
<td>Study population consists of patients treated with GCD-0449 in a previous phase I or phase II cancer study</td>
</tr>
<tr>
<td>LDE225 (oral)</td>
<td>Advanced solid tumor cancers; medulloblastoma; BCC</td>
<td>Dose-finding and safety study</td>
</tr>
<tr>
<td>LDE225 (oral); placebo</td>
<td>Gorlin syndrome</td>
<td>Placebo-controlled efficacy, safety, and pharmacokinetics study</td>
</tr>
<tr>
<td>LDE225 (oral)</td>
<td>Medulloblastoma; rhabdomyosarcoma; neuroblastoma; hepatoblastoma; high-grade glioma; astrocytoma</td>
<td>Dose-finding and safety study in children</td>
</tr>
<tr>
<td>LDE225</td>
<td>Advanced solid tumor cancers; medulloblastoma; BCC</td>
<td>East Asian study</td>
</tr>
<tr>
<td>LDE225 0.25% (topical); LDE225 0.75% (topical); placebo</td>
<td>BCC in Gorlin syndrome</td>
<td>Placebo-controlled study of safety, local tolerability, pharmacokinetics, and pharmacodynamics</td>
</tr>
<tr>
<td>LEQ506 (oral)</td>
<td>Advanced solid tumors; recurrent or refractory medulloblastoma; locally advanced or metastatic BCC</td>
<td>Dose-finding and safety study</td>
</tr>
<tr>
<td>LEQ506</td>
<td>Advanced solid tumors (recurrent or refractory medulloblastoma; locally advanced or metastatic BCC)</td>
<td></td>
</tr>
<tr>
<td>BMS-833923 (XL139)</td>
<td>Advanced or metastatic cancer; BCC; Gorlin syndrome</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Clinicaltrials.gov.*

BCC=basal cell carcinoma; CNS=central nervous system; FOLFIRI=folinic acid (leucovorin), fluorouracil (5-FU), irinotecan; FOLFOX=folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin.

*Note that this information is current as of December 1, 2011. Early clinical trials represent a dynamic and sometimes rapidly changing process. Updated information can be accessed at http://clinicaltrials.gov.
Five other Smoothened pathway inhibitors have been developed: BMS-833923, GDC-0449, IPI926, LDE225, and, TAK-441; several of these are being tested in cancers other than BCC, and some are being tested in combination with chemotherapeutic agents and/or regimens. Table 2 summarizes the Smoothened inhibitors currently in phase I and II clinical trials involving patients with sporadic BCCs as well as those with Gorlin syndrome who have BCCs, medulloblastomas, or other cancers.

## Conclusion

Patients with a few, sporadic BCCs that are identified and treated early will almost always have complete clearance and low risk of recurrence when treated with the modalities currently available, provided that these are appropriately chosen and skillfully applied.

Patients with many BCCs, such as those with Gorlin syndrome or ionizing radiation damage, have had little choice but to undergo multiple surgical procedures. For these patients and for the occasional individuals with BCC tumors that are large, advanced, refractory to treatment, or recurrent, recent advances in targeted therapies hold great promise for improved treatments and associated improvements in quality of life.

A number of targeted therapies currently are in clinical trials. The agents that seem to be most likely to be effective in BCC are the class of Smoothened pathway inhibitors. One, in particular, the Smoothened pathway inhibitor known as GDC-0449 (vismodegib), is well along in development, having recently begun phase III trials. However, early indications are that tumors may develop resistance over time to some of these new treatments. For this reason, researchers and clinicians alike anticipate the development and potential availability of as many effective treatments as possible, to allow patients the greatest chances for successful outcomes over the long term.

## References

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. Please print.

Name: ____________________________

Specialty: ____________________________

Degree: MD, DO, PharmD, DPh, PhD, BS, BA, Other

Affiliation: ____________________________

Address: ____________________________

City: ____________________________ State: ____________________________ ZIP: __________

Telephone: ____________________________ Fax: ____________________________

E-mail: ____________________________

Signature: ____________________________

CME CREDIT VERIFICATION
I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 2.0 CME credit(s) will be issued for this activity.

COURSE EVALUATION: GAPS
This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

- Diagnosing and treating advanced cases of basal cell carcinoma.
- Using therapeutic options in the treatment of severely affected basal cell carcinoma patients.
- Identifying the role that the Hedgehog signaling pathway plays in the development of cancer.
- Describe an emerging pharmacologic class that may be able to target the Hedgehog pathway.

Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
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Please elaborate on your answer.

Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?

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<tr>
<th>Strongly Agree</th>
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Please elaborate on your answer.

What topics do you want to hear about more, and what issue(s) in your practice will they address?

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Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed on the left?

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Please elaborate on your answer.

Were the patient recommendations based on acceptable practices in medicine?

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If no, please explain which recommendation(s) were not based on acceptable practices in medicine.

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If no, please list the article(s) that was/were biased.

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