Review Article

Metastatic Basal Cell Carcinoma in the Era of Hedgehog Signaling Pathway Inhibitors

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BACKGROUND: Inhibition of the hedgehog signaling pathway (HHSP) for the treatment of locally advanced basal cell carcinoma (BCC) and metastatic BCC (mBCC) has produced promising results. Typically, mBCC is not taken into consideration during the workup of a patient with multifocal metastatic disease who has a history of BCC. The objective of the current review, in which the authors evaluated the time from the first BCC diagnosis to metastasis, location of disease, and radiographic features, was to contribute to the general knowledge and awareness among providers, patients, and support groups about mBCC and to provide an outlook for the future of treatments for mBCC. A literature review on mBCC and a review of records from patients with mBCC who presented to Virginia G. Piper Cancer Center Clinical Trials (an oncology clinical trials center) were conducted. The clinical and radiographic findings of 22 patients with mBCC who were evaluated at that center from the initiation of smoothened (SMO) antagonist trials were analyzed along with a review of BCC epidemiology and pathogenesis, the HHSP, and current and future treatments for this rare presentation of the most common malignancy. The results indicated that, in the last 5 years, there has been a plethora of new agents targeting SMO, a key component of the HHSP that, for the majority of patients with mBCC, may be a good match for targeting tumor genetic vulnerability. Like with other targeted therapy for uncommon malignancies, such as chronic myelogenous leukemia and gastrointestinal stromal tumors, the authors anticipate that there will be clinical development of next-generation HHSP inhibitors to combat mBCCs that are nonresponsive to or progress on current SMO antagonists. ***Cancer*** **2012;118:5310-9.**

KEYWORDS: metastatic basal cell carcinoma, nevoid basal cell carcinoma syndrome, computerized tomography, positron emission test, hedgehog signaling pathway.

INTRODUCTION

In the last several years, inhibition of the hedgehog signaling pathway (HHSP) for the treatment of locally advanced basal cell carcinoma (BCC) and metastatic BCC (mBCC) has led to a potential revolutionary change in how advanced BCC is treated. Patients with unresectable and/or mBCC are now personally seeking or being referred for clinical trial evaluation involving inhibitors of smoothened (SMO). Whereas BCC of the skin is the most common malignancy with over 1.4 million cases per year in the United States alone,[1-3] mBCC is rare with an estimated incidence of <0.003% to 0.5%.[4]

Consideration of mBCC often is not included in the typical workup of a patient with multifocal metastatic disease who has a history of BCC. It is our hope that the current review, which includes evaluation of the timing from first BCC to metastasis, disease location, and radiographic features of the patients, will contribute to general knowledge about mBCC and awareness among providers, patients, and support groups along with providing an outlook for the future of treating mBCC. This review focuses on the clinical and radiographic findings in 22 patients with mBCC who were evaluated at an oncology clinical trials center after the advent of clinical trials with a SMO antagonist, along with a discussion of BCC epidemiology and pathogenesis, the HHSP, and current and future treatments for this rare presentation of the most common malignancy.

Basal Cell Carcinoma Overview

BCC is the most common malignancy and is a skin cancer. It is believed that BCC originates from the basal layer of the epidermis, the interfollicular epidermis, and the hair follicle. By using mouse models, investigators demonstrated that multiple epithelial compartments in skin can form BCC-like tumors, and the subtype of BCC can be manipulated, depending on which epithelial compartment is altered.[5] It is estimated that approximately 65% to 75% of nonmelanoma skin cancer treated in the United States is BCC[1,2]; and, in 2006, 2.2 million nonmelanoma skin cancers were treated.[3]

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We thank the patients and clinic staff, including Daniel Von Hoff, Mitesh Borad, Raoul Tibes, Ramesh Ramanathan, Lisa Blaydorn, Molly Downhour, Katy Schroeder, Lisa Rumble, Karen Lewandowski, Barry Kruse, and Valerie George; and we thank Maya Hernandez and Curtis Thacker for their assistance with assembling scans for review.

DOI: 10.1002/cncr.27532, **Received:** December 20, 2011; **Revised:** February 10, 2012; **Accepted:** February 13, 2012, **Published online** April 17, 2012 in Wiley Online Library (wileyonlinelibrary.com)

Approximately 95% of individuals are diagnosed with BCC between ages 40 and 79 years.[6] BCC is much more common in Caucasians than individuals of African descent or dark-skinned populations.[6] The incidence is approximately 30% higher in men than in women.[7]

Close to 90% of BCCs occur in the head and neck region, and risk factors include fair skin pigmentation, radiation (ultraviolet and/or ionizing), exposure to arsenic or polycyclic aromatic hydrocarbons, immunosuppression, scars, and certain genetic syndromes, such as nevoid BCC syndrome (NBCCS).[8] A previous personal history of BCC leads to an increased risk of developing BCC in the future. BCC rates also are higher in individuals who live closer to the equator,[7,9] in the United States, and in other countries, such a Australia,[10] in contrast to Northern European countries like Finland, which have a relatively lower incidence of BCC.[11]

Nevoid Basal Cell Carcinoma Syndrome

NBCCS is a rare, autosomal-dominant, multisystem disorder with a prevalence of 1 in 57,000 to 256,000 individuals. It results from germline mutations in the Patched gene (*PTCH1*) located on chromosome 9q22.3.[12,13] Not all patients with NBCCS have detectable *PTCH1* mutations, suggesting the presence of mutations in other components of the HHSP.[14] NBCCS is more common in Caucasians but has been reported in individuals of African[12] and Asian decent.[15] Characterized by a wide range of developmental abnormalities and a predisposition to neoplasms, the main clinical manifestations of NBCCS include early onset of multiple BCCs (median age, 20 years),[12] odontogenic keratocysts of the mandible, palmar and plantar pitting, craniofacial anomalies, and skeletal abnormalities.[13] Approximately 5% to 10% of individuals with NBCCS may develop medulloblastoma.[13] An individual with NBCCS may have hundreds to thousands of BCCs treated, yet their life expectancy does not differ much from that of individuals without NBCCS.[13]

A diagnosis of NBCCS requires satisfactory clinical evidence of either 2 major criteria or 1 major and 2 minor criteria.[16] The radiographic diagnostic workup for NBCCS may include the following: a skull x-ray or computed tomography (CT) scan to identify calcified falx cerebri[16]; panoramic films to identify odontogenic keratocysts[17]; and chest, hand, and/or foot x-rays to identify other skeletal abnormalities.[16]

Basal Cell Carcinoma Aggressiveness: Histology Dependent

Many histologic variants of BCC have been characterized. Two main categories exist that subdivide BCC by their aggressiveness. BCCs with *nonaggressive growth patterns* include nodular, superficial, and adnexal variants; whereas BCC with *aggressive growth patterns* include metatypical/basosquamous, morpheaform, infiltrating, sclerosing, and micronodular variants.[6,18,19] It is noteworthy that, in mouse models, postnatal induction of the glioblastoma protein 2 (GLI2) activator in telogen follicle stem cells leads to the development of nodular BCC-like skin tumors.[5] However, when the GLI2 activator is induced in the interfollicular epidermis or epidermis from hairless skin, superficial BCC-like tumors arise.[5] In contrast to superficial BCCs, the hair follicle is a potential site of origin for nodular BCC in mice.[5] In addition, the level of GLI2 activator can drive the development of nodular BCC-like tumors.[5]

Human BCC may also contain an admixture of histologies that fit into both growth pattern categories. Nearly all *mixed category* BCC originate in the head and neck region.[18] Because there are mixed category BCC in humans and hair follicle stem cell progeny migrate into the epidermis during wound healing, murine models suggest an explanation of this with the possibility of nodular BCC tumors expanding upward to involve the epidermis as a superficial BCC.[5] Detailed description and images of distinct features of BCC variants are beyond the scope of this review.[6,8,19]

In recurrent mixed category BCCs, it is the aggressive growth pattern variant that appears to predominate the patient's disease course.[18] The incidence of mixed category BCC can range from 11% to 43%. In >85% of these tumors, the aggressive growth pattern features may be unsuspected.[18] In other words, it is believed that the patient has a BCC variant with only nonaggressive growth pattern features based on the initial histopathologic assessment. This can lead to inadequate initial therapy, resulting in recurrent BCC and causing additional morbidity. Of the multiple modalities that can be used to treat primary BCC, each possesses differing rates of success (no BCC recurrence). Mohs' micrographic surgery has the highest rate of success, with a recurrence rate up to 3.3% rate.[18]

Metastatic Basal Cell Carcinoma

mBCC is exceedingly rare: The most conservative estimated rate is approximately 0.0028% or 28 cases per 1,000,000 BCC diagnoses, but the incidence has been cited as high as 0.5%.[4] Thus, annually, the most conservative estimated rate of mBCC is approximately 40 cases per year in the United States.[2,3,20] Nearly all reported cases of mBCC have been in Caucasians, and few individuals of

Table 1. Diagnostic Criteria for Metastatic Basal Cell Carcinoma

Criteria[a]
1. Primary tumor originated in the epidermis or follicular skin
2. Tumor spread to a distant site, not local extension
3. Both primary and metastatic tumors have the histologic appearance of BCC but not solely squamous cell histology

Abbreviations: BCC, basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
[a] To be considered mBCC, all 3 criteria must be met.

African or Asian decent diagnosed with mBCC have been reported in the literature.[21-23]

In 1951, diagnostic criteria for mBCC were defined by Lattes and Kessler[24] (Table 1). In mBCC, squamous features/differentiation appear to be more frequent than in primary BCC. However, as long as there are elements of BCC in the pathologic specimen, the diagnosis should remain classified as mBCC rather than metastatic squamous cell carcinoma.[25] mBCC can spread through subcutaneous infiltration, hematologically, or, in approximately 70% of cases, through the lymphatic system.[4,27] Nearly all histologic variants of BCC have been reported in mBCC based on recent data from mixed category BCC[18] and >80% of mBCC originate from primary BCC of the head and neck.[25] Thus, we wonder whether nonaggressive variants may transform to aggressive histologic variants during disease progression. We suspect that the undetected aggressive growth pattern in most mBCCs may explain why nonaggressive histologies, such as superficial or nodular types, have been associated with mBCC. Future research may clarify this issue.

Features of the Metastatic Basal Cell Carcinoma Patient Cohort

In total, 22 individuals with mBCC were evaluated (Tables 2 and 3). The majority of these patients traveled a distance even as much as >3300 miles (1 way). Of the 22 patients, there were 18 were men, and 10 patients had other family members with BCCs. Five of these individuals had confirmed NBCCS. The median age at first BCC diagnoses was approximately 43 years (range, 14-68 years). The majority of patients had primary BCC originating in the head and neck region.

Of 14 patients with primary BCC who had pathology reports that could be classified by variant, 1 patient had nonaggressive growth pattern features (nodular), 6 patients fulfilled the mixed category classification, and 7 patients had aggressive growth pattern features. The median time to developing mBCC was approximately 9 years (range, 1-48 years). The median age of the patients with mBCC was approximately 56 years (range, 46-89 years). Only 5 of 22 patients had no tumor or previous treatment-related symptoms at the time of their initial consultation. All but 1 patient had received previous BCC-related therapy, including surgery, radiotherapy, and/or chemotherapy. The sites of frequent mBCC involvement included lymph nodes, lung, skin, and bone. Other less common involved sites included pleura, liver, and brain. These results are similar to those reported in case series reviews (see Table 3) with a few exceptions. Our cohort had a higher prevalence of men with mBCC and a lower percentage with primary BCC involving the head/face; however, this may be because of our relatively smaller sample size. Finally, our cohort had a higher prevalence of lymph node and lung involvement, possibly because of improved imaging modalities compared with series reports preceding the 1990s. Imaging modalities like CT and 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scanning now allow for more accurate assessment of disease extent of mBCC than ever before.

Radiographic Findings of Metastatic Basal Cell Carcinoma

Computerized tomography

All CT imaging features were assessed before patients received SMO antagonist therapy. Most patients with mBCC who were evaluated by CT scans had multiple sites of disease (Fig. 1a-f). Only a limited number of organ systems had metastases identified, as noted in Table 4. BCC metastases had variable appearances on CT imaging. Individual metastatic lesions ranged in size from a few millimeters to several centimeters. The CT densities of the tumor lesions generally were solid, but necrosis and cystic changes were not uncommon.

Most metastatic disease either was centered within the skin and surrounding soft tissue and lymphatic system or spread hematogenously to the lungs, pleura, or bone. It is noteworthy, however, that the frequency of liver involvement was relatively low (1 patient had multiple liver metastases that measured approximately 1 cm in greatest dimension, and the other patient had small-volume serosal liver metastases) compared with lung and bone involvement. The attributes of mBCC that potentiated differential spread by lymphatics in 1 patient or through blood circulation in another have yet to be elucidated.

Skin and soft tissue involvement fell into 3 pattern types on CT imaging, including 1) an infiltrative pattern with loss of adjacent soft tissue planes (N = 5), 2) a nodular pattern with relatively well preserved tumor margins

Table 2. Detailed Clinical Features of the Current Metastatic Basal Cell Carcinoma Cohort

Patient	Age at First BCC, y	Sex	Family History	Histology Before Metastasis	Initial Location	Time to Metastasis, y	Prior Surgery/ XRT	Prior Chemotherapy	Age at VGPCC Consultation, y	Symptoms at VGPCC Consultation	Best Response to Hedgehog Inhibitor
1	~20	Man	Mother, brother, sisters, NBCCS (self)	Nodular[a]	Multiple locations	~28	Yes/yes	No	53	Sequelae of surgery and RT	PR
2	41	Man	No	Sclerosing	Neck	6.5	Yes/no	No	49	No	PR
3	43	Man	Brother	Basosquamous	Back	2	Yes/no	C+P, D, PI3K inhibitor	49	Fatigue, sequelae of surgery	PR
4	43	Woman	No	Nodular, infiltrating	Left cheek	3	Yes/no	No	48	Fatigue, TRP	PR
5	43	Man	No	Basaloid	Left periorbital	9	Yes/yes	HSP90 inhibitor	67	Dyspnea, TRP	PR
6	14	Man	No	BCC NOS	Chin	~35	Yes/no	No	56	Bone pain	SD
7	24	Man	Brother	NA	Neck/back	34	Yes/yes	C+P, D+B, C+P+B	63	Bone pain, fatigue	NA
8	~33	Man	No	Sclerosing	Neck	~20	Yes/yes	Cis+P, Cis+cetuximab, 5-FU	53	Sequelae of surgery and RT	SD
9	~58	Man	N/A	Basosquamous	Neck	~4	Yes/yes	C+D, G+D, G+A, multityrosine kinase inhibitor to EGFR, HER2, VEGF, EPHB4, high-dose vitamin C	65	Sequelae of surgery and RT	SD
10	~19	Man	Father, NBCCS (self)	Basosquamous	Back	~48	Yes/yes	C+P+G, cetuximab, celecoxib	69	TRP	SD
11	68	Man	Two siblings	Nodular, basaloid with squamous differentiation	Back	7	Yes/no	No	75	No	SD
12	47	Man	No	Basal cell carcinoma NOS	Back	3.5	Yes/no	No	55	No	SD
13	17	Man	Daughter, NBCCS (self)	NA	Multiple locations	40	Yes/no	5-FU, Cis	57	Decreased hearing	SD
14	27	Man	Father, NBCCS (self)	Morpheaform	Back	13	Yes/yes	Cis, C+P, erlotinib, bortezomib+ cetuximab, A, G+B+Cape, Nab-paclitaxel+ sunitinib, pazopanib+ ixebepilone	47	Dyspnea, TRP, fatigue, sequelae of surgery and RT	SD
15	58	Woman	No	Invasive	Back	4	No/no	No	62	Fatigue, weight loss, TRP	PR
16	69	Man	No	Nodular, infiltrating	Scalp	20	Yes/no	No	89	TRP	PD
17	38	Man	Brother, father	Basaloid	Neck	5	Yes/no	C+P	46	No	NA
18	42	Woman	No	Invasive	Chest	8	No/no	No	50	Fatigue	PD
19	~44	Man	Brother, NBCCS (self)	Nodular, infiltrating[a]	Multiple locations	~30	Yes/no	No	74	Cough, weight loss	SD
20	54	Women	Brother	Morpheaform, infiltrating	Back	3	Yes/yes	No	59	TRP	PR
21	35	Man	No	Sclerosing, infiltrating	Scalp	15	Yes/yes	No	50	N	SD
22	52	Man	No	Basosquamous	Chin	1[b]	Yes/no	No	53	TRP, fatigue, sequelae of surgery	PR

Abbreviations: 5FU, 5-fluorouracil; A, pemetrexed; B, bevacizumab; BCC, basal cell carcinoma; BCC, basal cell carcinoma; C, carboplatin; Cape, capecitabine; Cis, cisplatin; D, docetaxel; EGFR, epidermal growth factor receptor; EPHB4, ephrin type-B receptor 4; G, gemcitabine; HER2, human epidermal growth factor receptor 2; HSP90, heat shock protein 90; NA, not available or applicable; Nab-paclitaxel, nanoparticle albumin-bound paclitaxel; NBCCS, nevoid basal cell carcinoma syndrome; NOS, not otherwise specified; P, paclitaxel; PD, progressive disease; PI3K, phosphoinositide 3-kinase; PR, partial response; RT, radiotherapy; SD, stable disease; TRP, tumor-related pain; VEGF, vascular endothelial growth factor; VGPCC, Virginia G. Piper Cancer Center; XRT, external-beam radiotherapy; y, years.

[a] This was the histologic subtype of all biopsied BCCs immediately preceding metastasis.

[b] Metastases may have been present at initial diagnosis; however, complete staging imaging was not done until the patient was evaluated at an oncology clinical trials center.

Table 3. Clinical Features of Metastatic Basal Cell Carcinoma From the Literature and the Current Cohort

Variable	Data From the Literature	Current Cohort
Total no. of patients	N = 170[a]	N = 22
Men:women	2:1	4.5:1
Age at onset of primary BCC: Median (range), y	45 (14-84)	43 (14-68)
Interval to mBCC: Median (range), y	9 (0-45)	9 (1-48)
Age at mBCC diagnosis: Median (range), y	59 (24-89)	56 (46-89)[b]
Most frequent site of primary BCC preceding mBCC, %		
Total no. of patients	N = 159	N = 22
Head/face	67.6	36.9
Trunk	16.5	36.9
Extremities	6.4	—
Neck	2.4	26.2
Most frequent site of mBCC, %		
Lymph node	55.3	63.7
Lung	34.6	59.1
Bone	27.7	36.4
Skin	11.9	45.5[c]
Liver	9.4	9.1
Type of prior therapy for BCC, %		
No. of patients	N = 77[d]	N = 22
Surgery	84.4	90.9
Radiotherapy	29.8	40.9
Systemic therapy	NA	40.9
None	7.8	4.5

Abbreviations: BCC, basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NA, not available.
[a] See von Domarus & Stevens 1984.[25]
[b] Age with mBCC at consultation for the current cohort.
[c] Radiographic evidence of skin involvement was observed either as a single site or as multifocal sites with concurrent BCC involvement of a metastatic site.
[d] See Corcoran & Scott 2006.[26]

(N = 3), or 3) a mixed pattern (N = 1). The necrosis within lesions sometimes was observed, particularly in tumors with a nodular pattern.

Pulmonary disease on CT scans ranged from multiple lesions (1-3 metastases) to widespread parenchymal disease. The lesions tended to form coalescent masses in the lungs. Most lesions had spiculated margins, especially when they were large, whereas the smaller lesions (<1 cm in greatest dimension) tended to be more rounded and well defined. Central necrosis often was observed within the larger lesions, but cavitation was rare. All pulmonary segments were involved without a propensity for the right or left lung. Volume loss occasionally was observed in the setting of conglomerate lesions, suggesting a component of fibrosis and retraction. Pleural disease was noted in 18% of patients, usually in the form of moderate-to-large effusions. Nodular pleural disease was noted in 1 patient.

Bone lesions were identified in 8 of 22 patients (36%). Their appearance on CT scans varied from subtle osteolytic lesions (observed only on retrospect with PET/CT imaging in 1 patient), to mixed osteolytic and osteoblastic changes (similar to those noted in more common tumors, such as breast cancer), to destructive processes with a soft tissue component in 4 patients.

Lymph node involvement included predominately the neck (N = 6), axilla (N = 5), and chest lymph node stations (N = 8). Multiple lymph node station involvement was common (10 of 14 patients). The lymph nodes tended to have infiltrating margins and/or central low density on Hounsfield CT measurements, suggesting necrosis. Hyperenhancement was rare on contrast-enhanced CT images (N = 1).

Positron emission tomography/computed tomography imaging

All PET/CT imaging features were assessed before patients received SMO antagonist therapy. Very little is known about the FDG metabolic behavior of BCC metastasis. In theory, PET/CT images should be able to provide information that is complementary to that provided by conventional imaging techniques because of the functional nature of PET/CT scanning and whole-body surveys for disease. Hypermetabolic primary BCC originating in the head and neck region has previously been reported.[28]

In our cohort, we noted that patients who underwent PET/CT imaging had hypermetabolic activity in BCC lesions (Fig. 2a-e). Indeed, at least 1 hypermetabolic lesion was observed in every patient who had a baseline PET/CT scan before the initiation of SMO antagonist therapy. The peak FDG activity, measured as the maximal standardized uptake value (SUV_{max}), ranged from 1.9 to 16.8 (mean SUV_{max}, 7.3). Typically, this value was 2 to 4 times above background tissue metabolism. The distribution of FDG-avid disease within organ systems was nearly identical to that observed on contrast-enhanced CT images in those patients who underwent both types of imaging examinations. However, hepatic disease was not observed on PET/CT images in the 1 patient who had serosal disease on a CT scan. This may be because of the relatively small size and serosal nature of this patient's hepatic disease. PET/CT images tended to demonstrate more disease in bone and soft tissues compared with contrast-enhanced CT images, likely because of whole-body coverage with PET/CT scanning and the often subtle changes in the osseous structures involved in bone metastasis.

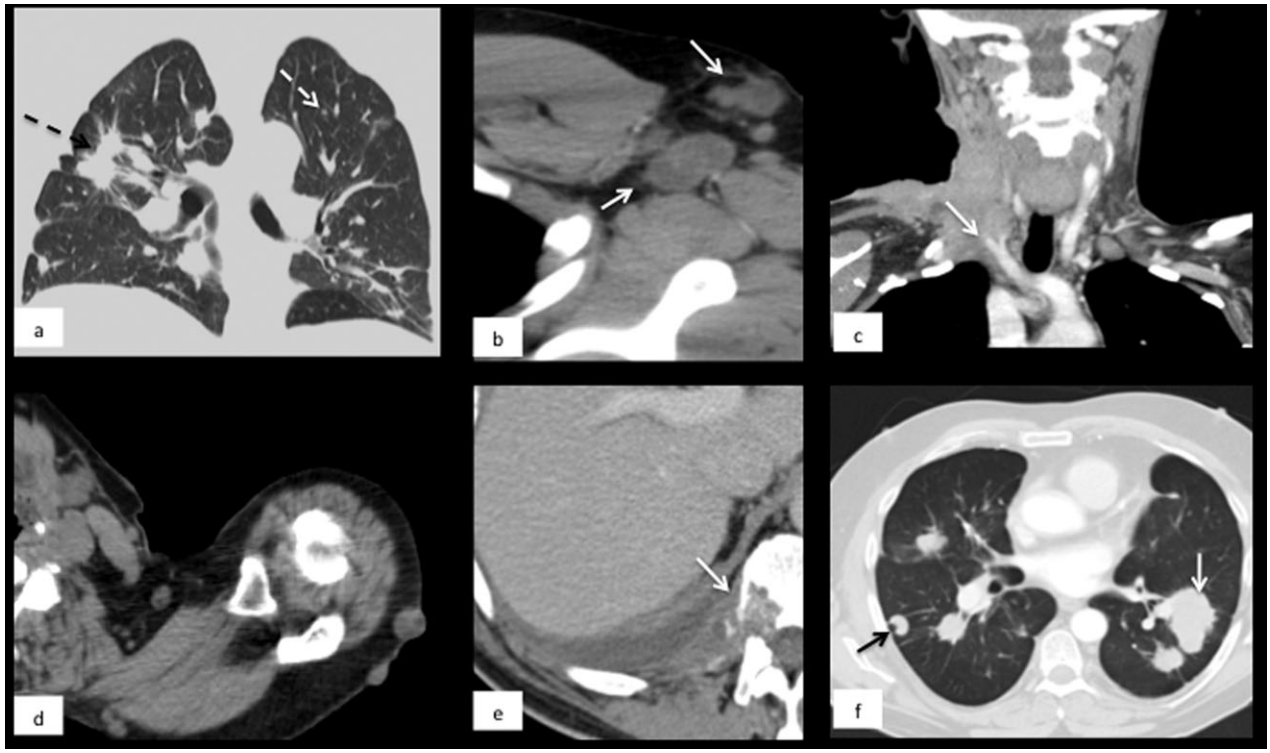

Figure 1. Basal cell carcinoma (BCC) metastases are observed on computed tomography (CT) images. (a) This coronal CT image of the chest reveals multiple pulmonary metastases ranging in size from 1 mm to 6.5 cm (dashed arrows). (b) An axial CT image of the left axilla demonstrates low-density lymph node (necrotic) involvement (arrows). (c) A coronal contrast-enhanced CT image of the neck reveals an infiltrative BCC skin lesion that is invading the right carotid arteries with extension of the mass into the right lung apex (arrow). (d) An axial CT image of the left shoulder demonstrates nodular skin lesion. (e) This axial CT image of the chest reveals bone metastasis with extraosseous extension of tumor into the right extrapleural space. The right pleural effusion suggests pleural involvement with BCC. (f) Another axial CT image of the chest reveals multiple pulmonary metastases that are both rounded and smooth (black arrow) to spiculated and clustered (white arrow).

Table 4. Metastatic Basal Cell Carcinoma: Radiographic Sites of Involvement

Organ/Site Involvement	No. of Patients, N = 22
Lymph nodes	14
Pulmonary	13
Skin/soft tissue[a]	10
Bone	8
Pleura	4
Hepatic	2
Brain	1

[a] Radiographic evidence of skin involvement was observed either as a single site or as multifocal sites with concurrent basal cell carcinoma involvement of a metastatic site.

Contrast-enhanced CT images tended to demonstrate more disease in the lung, especially in lesions that measured <7 mm. Failure to detect very small lung parenchymal lesions is a known limitation of PET/CT imaging. Nevertheless, PET/CT screening for patients with mBCC may be helpful to fully evaluate disease burden and to potentially measure therapeutic response.

Staging Workup and Treatment

The tumor, lymph node, metastasis (TNM) staging system is used commonly for most malignancies. A TNM staging system endorsed by the American Joint Committee on Cancer (AJCC) is available.[29] When possible, for locally advanced BCC and mBCC, the TNM staging may enable better prognostication as newer systemic treatment modalities become commercially available and as awareness about advanced BCC increases.

Molecular Pathogenesis of Metastatic Basal Cell Carcinoma

Similar to primary BCC and NBCCS, the main genetic aberration in mBCC is most commonly the result of mutations or loss of heterozygosity (LOH) of the tumor suppressor *PTCH1*.[30] In addition, mutations in smoothened (*SMO*) or mutations or LOH of *PTCH2* also can lead to basal cell carcinogenesis.[31-33] Together, these perturbations account for up to 95% of basal cell carcinogenesis.[32,33] In addition, *TP53* gene mutations are identified in >50% of BCCs, although these probably

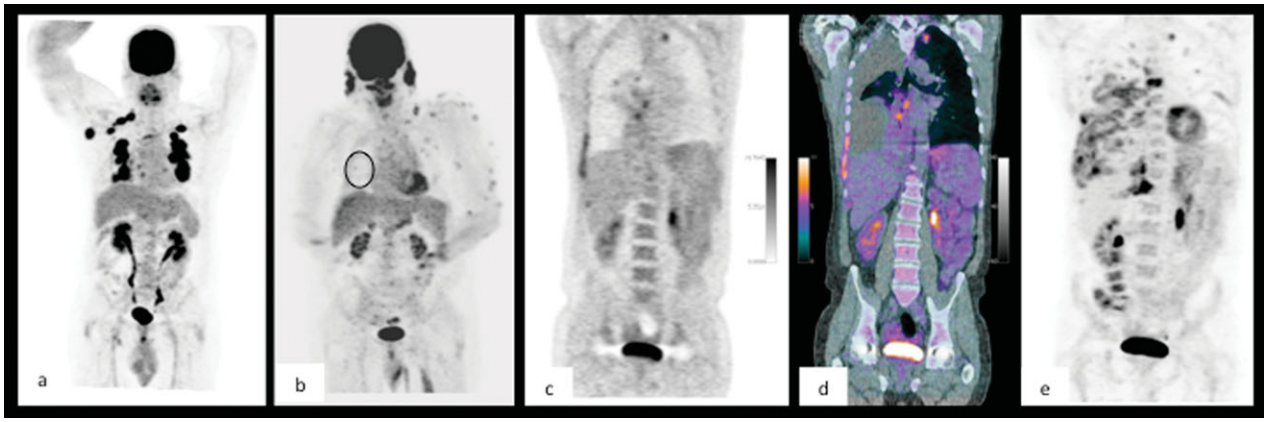

Figure 2. Basal cell carcinoma is observed on ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) images. Three different patients are shown. (a) This maximum-intensity projection (MIP) PET image reveals the intense FDG activity in conglomerate masses within the chest and right axilla. This image illustrates both the lymphatic and hematogenous nature of the metastatic disease. (b) An MIP PET image from a different patient reveals both bilateral neck involvement and nodular skin involvement in the left upper extremity. Note the range of FDG activity from faint to robust. Standardized uptake values ranged from 1.9 (black circle) to 16.8 in this cohort of patients. These images are (c) coronal PET, (d) fused PET/CT, (e) and MIP PET studies that reveal extensive disease in the lungs, mediastinal lymph nodes, pleural space, and bones. PET/CT imaging has the advantage of providing whole-body imaging in the assessment of disease burden compared with CT.

are related to disease progression rather than carcinogenesis.[32] PTCH1, PTCH2, and SMO are all components of the HHSP, which has several therapeutics currently in clinical development.

The Hedgehog Signaling Pathway

Targeting of the HHSP as an anticancer therapy is a fairly recent concept. The impetus that led to the HHSP discovery and characterization began with the initial observation of severe holoprosencenphaly and other congenital malformations in newborn lambs after pregnant ewes consumed California corn lily (*Veratrum californicum*) in 1962.[34] The cause of these teratogenic effects was a chemical aptly named cyclopamine.[35] Whereas normal HHSP signaling is involved in cell growth and congenital development,[36,37] is has been proposed that dysregulated HHSP signaling involves nearly 25% of malignancies.[36] Ensuing research led to the demonstration that cyclopamine or synthetic HHSP pathway inhibitors potentially could be useful to inhibit HHSP signaling in malignancy.[38]

The main ligand that activates the HHSP pathway is Sonic.[33,39,40] Signaling is initiated when Sonic binds to its receptor, PTCH1, and inactivates it.[33,39,40] A series of events ensue, including disinhibition of the transmembrane domain protein SMO. SMO migrates to primary cilia and enables GLI activator,[41] leading to transcriptional up-regulation of target genes.[42] Without HHSP ligand signaling, PTCH1 remains activated, inhibiting SMO, leading to GLI repressor, such that HHSP target gene transcription is blocked (for further details, see Weiss and Von Hoff, 2010[33]).

In cancers with *PTCH1*-activating and/or *SMO*-activating mutations, HHSP signaling is ligand-independent (Type I system) and, thus, does not require Sonic binding to PTCH1. Tumors comprising the Type I system include BCC, medulloblastomas, and rare variants of rhabdomyosarcoma.[33,40] The HHSP ligand-dependent autocrine cancers (Type II system) include breast, pancreas, lung, prostate, upper gastrointestinal, melanoma, and colorectal cancers.[33,40] The HHSP ligand-dependent paracrine cancers (Type III system) include colorectal, pancreas, and prostate cancers.[33,40]

For the most part, in the pre-HHSP inhibitor era, treatment largely has been disappointing, with a median survival of 8 months (range, 0-192 months).[25] By using cisplatin-based therapy, some individuals have enjoyed prolonged disease-free survival.[43-46]

Targeting the Hedghog Signaling Pathway With Smoothed Antagonists

Targeting the HHSP in cancer therapeutics is an active field in drug development. Recently, vismodegib (GDC-0449) was approved by the US Food and Drug Administration for treating BCC that has recurred after surgery or that has advanced locally or metastasized. There are now at least 7 additional SMO antagonists in various stages of clinical trial development, including BMS-833923, IPI-926, LDE-225, PF-04449913, LEQ506, TAK-441, and LY2940680. The most impressive and positive, life-altering results from these therapeutic trials in patients with metastatic cancer have

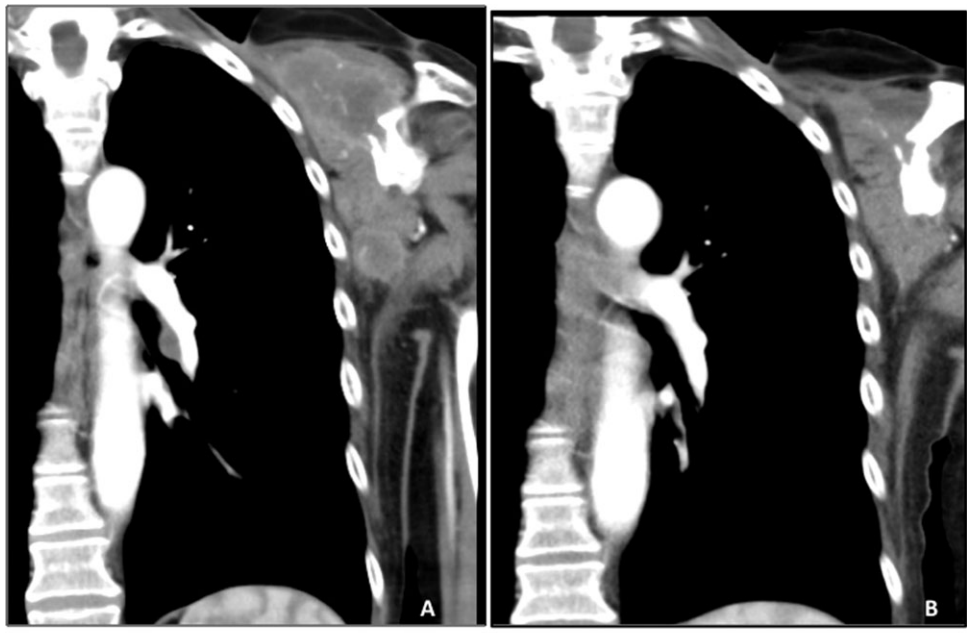

Figure 3. Treatment response to *Smoothened* (SMO) antagonist therapy is illustrated. (a) A coronal computed tomography (CT) image of the chest reveals a large soft tissue lesion involving the left scapula before the initiation of SMO antagonist therapy. (b) This coronal CT image of the chest after approximately 2 months of SMO antagonist treatment reveals a significant reduction (partial response) in tumor burden.

been document in mBCC. At least 2 SMO antagonists have undergone phase 2 evaluation in advanced BCC trials.[47]

The first human results in advanced/mBCC demonstrating a response to vismodegib were published in 2009.[30] Overall, this agent is well tolerated with primarily mild-to-moderate side effects, including dysguesia, hair loss, and muscle cramps.[48] Subsequently, the single-arm phase 2 results of vismodegib in mBCC (N = 33) recently were announced, and the agent demonstrated a 30% response rate and a median progression-free survival of 9.5 months.[49] Results for LDE225, the other SMO antagonist in phase 2 trials for advanced BCC, are still too early to report. However, in the phase 1 study, 5 patients with advanced BCC attained at least a partial response, and at least 2 patients were on therapy for >4 months.[50]

In total, 20 patients with mBCC in this cohort (Table 2) received treatment with SMO antagonists. The best response achieved was a partial response in 8 patients (for a representative example, see Fig. 3a,b), stable disease in 10 patients, and 2 patients had progressive disease as their best response to an SMO antagonist.

Other Drugs Targeting the Hedgehog Signaling Pathway

Other naturally occurring agents or drugs that have been approved for the treatment other diseases have demonstrated the ability to inhibit HHSP inhibition in preclinical studies.[51] Vitamin D3 (cholecalciferol) is a fat-soluble vitamin that can inhibit SMO and has greater potency than cyclopamine in vitro.[52] In preclinical models, drugs that inhibit GLI1 or forkhead box protein M1 (FOXM1), which are downstream of SMO, also have been reported. By targeting downstream of SMO, in theory, mBCC tumors that lack sensitizing genetic aberrations that would be responsive to SMO antagonists or mBCC tumors that develop resistance to SMO antagonists may derive benefit from these agents. Agents that target GLI1 include GLI antagonist 61 (GANT61)[53] and arsenic trioxide.[54] AY9944, a diamine substructure of GANT61 and an inhibitor of the enzymatic activity and transcriptional inducer of 7-dehydrocholesterol reductase (Dhcr7), can attenuate HHSP signaling when there is up-regulation of endogenous Dhcr7.[55] Thus, other Dhcr7 modulators, such as the antidepressant imipramine and antipsychotics like clozapine, chlorpromazine, and haloperidol; can regulate HHSP signaling.[55] Itraconazole, an antifungal agent, also inhibited GLI in a reporter assay.[56] In fact, a trial of oral or topical itraconazole in nonmetastatic BCC is underway (National Clinical Trial NCT01108094). Agents that target FOXM1 include thiazole antibiotics like siomycin A and proteosome inhibitors like bortezomib.[51] Statins and human 3-hydroxy-3-methylglutaryl-coenzyme

A reductase inhibitors, which are approved to prevent and treat heart disease by lowering blood cholesterol, also were able to reduce HHSP target gene transcription and pathway-dependent proliferation in medulloblastoma in vitro.[57]

In conclusion, during the last 5 years, there has been a plethora of new agents targeting SMO, a key component of the HHSP. For the majority of mBCCs, SMO antagonists should be a great context in which to match a targeted agent to tumor genetic vulnerability. The emergence of disease progression in mBCC caused either by selection for resistant tumor clones or by the development of acquired resistance is a real clinical problem for patients with mBCC.[33,57] Like in other targeted therapies for uncommon malignancies, such as chronic myelogenous leukemia and gastrointestinal stromal tumors, it is likely that next-generation HHSP inhibitors will be introduced to combat mBCC in patients who are nonresponsive or who progress on current SMO antagonists. With improved awareness of mBCC, we hope that, at the least, patients who have this very rare cancer are considered for referral to a cancer center that is investigating SMO antagonists in mBCC or in advanced solid tumors.

FUNDING SOURCES

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

G.J.W. is a principal investigator or coinvestigator on trials involving hedgehog pathway inhibitors in cancer with Genentech, Infinity Pharmaceuticals, Novartis, and Eli Lilly. These companies provide funding to his institution. G.J.W. is also on the Speaker's Bureaus of Eli Lilly and Genentech.

REFERENCES

1. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol.* 1994;30:774-778.
2. Malone JP, Fedok FG, Belchis DA, Maloney ME. Basal cell carcinoma metastatic to the parotid: report of a new case and review of the literature. *Ear Nose Throat J.* 2000;79:511-515, 518-519.
3. American Cancer Society Cancer. Facts and Figures, 2011. Available at: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011. Accessed on July 31, 2011.
4. Ozgediz D, Smith EB, Zheng J, Otero J, Tabatabai ZL, Corvera,CU. Basal cell carcinoma does metastasize [serial online]. *Dermatol Online J.* 2008;14:5.
5. Grachtchouk M, Pero J, Yang SH, et al. Basal cell carcinomas in mice arise from hair follicle stem cells and multiple epithelial progenitor populations. *J Clin Invest.* 2011;121:1768-1781.
6. McGuire JF, Ge NN, Dyson S. Nonmelanoma skin cancer of the head and neck. I: histopathology and clinical behavior. *Am J Otolaryngol.* 2009;30:121-133.
7. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma. A population-based incidence study in Rochester, Minnesota. *J Am Acad Dermatol.* 1990;22:413-417.
8. Buljan M, Bulat V, Situm M, Mihic LL, Stanic-Dukta JS. Variations in clinical presentation of basal cell carcinoma. *Acta Clin Croat.* 2008;47:25-30.
9. Reizner GT, Chuang TY, Elpern DJ, Stone JL, Farmer ER. Basal cell carcinoma in Kauai, Hawaii: the highest documented incidence in the United States. *J Am Acad Dermatol.* 1993;29:184-189.
10. Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer.* 1993;20:585-590.
11. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. *Arch Dermatol.* 1999;135:781-786.
12. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet.* 1997;69:299-308.
13. Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome) [serial online]. *Orphanet J Rare Dis.* 2008;3:32.
14. Endo M, Fujii K, Miyashita T, et al. PTCH1 gene analysis in 25 Japanese patients with Gorlin syndrome [article in Japanese]. *No To Hattatsu.* 2009;41:259-263.
15. Tanabe R, Fujii K, Miyashita T, et al. Clinical manifestations in 25 Japanese patients with Gorlin syndrome [article in Japanese]. *No To Hattatsu.* 2009;41:253-257.
16. Kimonis VE, Mehta SG, Digiovanna JJ, Bale SJ, Pastakia B. Radiological features in 82 patients with nevoid basal cell carcinoma (NBCC or Gorlin) syndrome. *Genet Med.* 2004;6:495-502.
17. Palacios E, Serou M, Restrepo S, Rojas R. Odontogenic keratocysts in nevoid basal cell carcinoma (Gorlin's) syndrome: CT and MRI evaluation. *Ear Nose Throat J.* 2004;83:40-42.
18. Cohen PR, Schulze KE, Nelson BR. Basal cell carcinoma with mixed histology: a possible pathogenesis for recurrent skin cancer. *Dermatol Surg.* 2006;32:542-551.
19. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. *Mod Pathol.* 2006;19:S127-S147.
20. Wadhera A, Fazio M, Bricca G, Stanton O. Metastatic basal cell carcinoma: a case report and literature review. How accurate is our incidence data [serial online]? *Dermatol Online J.* 2006;12:7.
21. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol.* 1991;24:715-719.
22. Jahan-Tigh RR, Alston JL, Umphlett M. Basal cell carcinoma with metastasis to the lung in an African American man. *J Am Acad Dermatol.* 2010;63:87-89.
23. Seo SH, Shim WH, Shin DH, Kim YS, Sung HW. Pulmonary metastasis of basal cell carcinoma. *Ann Dermatol.* 2011;23:213-216.
24. Lattes R, Kessler RW. Metastasizing basal-cell epithelioma of the skin; report of 2 cases. *Cancer.* 1951;4:866-878.
25. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of 5 cases and review of 170 cases in the literature. *J Am Acad Dermatol.* 1984;10:1043-1060.
26. Corcoran RB, Scott MP. Oxysterols stimulate Sonic hedgehog signal transduction and proliferation of medulloblastoma cells. *Proc Natl Acad Sci U S A.* 2006;103:8408-8413.
27. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of 2 cases and literature review. *J Cutan Med Surg.* 2005;9:10-15.
28. Fosko SW, Hu W, Cook TF, Lowe VJ. Positron emission tomography for basal cell carcinoma of the head and neck. *Arch Dermatol.* 2003;139:1141-1146.
29. American Cancer Society. Skin Cancer: Basal and Squamous Cell. Available at: http://www.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-basal-and-squamous-cell-staging. [Access date.]
30. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med.* 2009;17:1164-1172.
31. Pan S, Dong Q, Sun LS, Li TJ. Mechanisms of inactivation of PTCH1 gene in nevoid basal cell carcinoma syndrome: modification of the 2-hit hypothesis. *Clin Cancer Res.* 2010;15:442-450.
32. Chinem VP, Miot HA. Epidemiology of basal cell carcinoma. *An Bras Dermatol.* 2011;86:292-305.
33. Weiss GJ, Von Hoff DD. Hunting the hedgehog pathway. *Clin Pharmacol Ther.* 2010;87:743-747.

34. Binns W, James LF, Shupe JL, Thacker EJ. Cyclopian-type malformation in lambs. *Arch Environ Health.* 1962;5:106-108.
35. Binns W, James LF, Shupe JL, Everett G. A congenital cyclopian-type malformation in lambs induced by maternal ingestion of a range plant, Veratrum californicum. *Am J Vet Res.* 1963;24:1164-1175.
36. Keeler RF, Binns W. Teratogenic compounds of Veratrum californicum (Durand). V. Comparison of cyclopian effects of steroidal alkaloids from the plant and structurally related compounds from other sources. *Teratology.* 1968;1:5-10.
37. Lum L, Beachy PA. The hedgehog response network: sensors, switches, and routers. *Science.* 2004;18:1755-1759.
38. Ma Y, Erkner A, Gong R, et al. Hedgehog-mediated patterning of the mammalian embryo requires transporter-like function of dispatched. *Cell.* 2002;4:63-75.
39. Cooper MK, Porter JA, Young KE, Beachy PA. Teratogen-mediated inhibition of target tissue response to shh signaling. *Science.* 1998;5:1603-1607.
40. Epstein EH. Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer.* 2008;8:743-754.
41. Scales SJ, de Sauvage FJ. Mechanisms of hedgehog pathway activation in cancer and implications for therapy. *Trends Pharmacol Sci.* 2009;30:303-312.
42. Ingham PW, Placzek M. Orchestrating ontogenesis: variations on a theme by sonic hedgehog. *Nat Rev Genet.* 2006;7:841-850.
43. Pfeiffer P, Hansen O, Rose C. Systemic cytotoxic therapy of basal cell carcinoma. A review of the literature. *Eur J Cancer.* 1990;26:73-77.
44. Wieman TJ, Shively EH, Woodcock TM. Responsiveness of metastatic basal-cell carcinoma to chemotherapy. A case report. *Cancer.* 1983;52:1583-1585.
45. Jefford M, Kiffer JD, Somers G, Daniel FJ, Davis ID. Metastatic basal cell carcinoma: rapid symptomatic response to cisplatin and paclitaxel. *ANZ J Surg.* 2004;74:704-705.
46. Carneiro BA, Watkin WG, Mehta UK, Brockstein BE. Metastatic basal cell carcinoma: complete response to chemotherapy and associated pure red cell aplasia. *Cancer Invest.* 2006;24:396-400.
47. National Institutes of Health. National clinical trials website. Available at: http://www.clinicaltrials.gov. Accessed December 16, 2011.
48. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. *Clin Cancer Res.* 2011;17:2502-2511.
49. Sekulic A, Migden MR, Oro AE, et al. A pivotal study evaluating efficacy and safety of the hedgehog pathway inhibitor (HPI) vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma (BCC). Paper presented at: Seventh European Association of Dermato-Oncology (EADO) Congress; June 20-23, 2011; Nantes, France. Abstract C014.
50. Tawbi HA, Ahnert JR, Dummer R, et al. Phase I study of LDE225 in advanced solid tumors: updated analysis of safety, preliminary efficacy, and pharmacokinetic-pharmacodynamic correlation [abstract]. *J Clin Oncol.* 2011;29(suppl). Abstract 3062.
51. So PL, Tang JY, Epstein EH. Novel investigational drugs for basal cell carcinoma. *Expert Opin Investig Drugs.* 2010;19:1099-1112.
52. Bijlsma MF, Spek CA, Zivkovic D, van de Water S, Rezaee F, Peppelenbosch MP. Repression of smoothened by patched-dependent (pro-)vitamin D3 secretion [serial online]. *PLoS Biol.* 2006;4:e232.
53. Mazumdar T, Devecchio J, Agyeman A, Shi T, Houghton JA. Blocking hedgehog survival signaling at the level of the GLI genes induces DNA damage and extensive cell death in human colon carcinoma cells. *Cancer Res.* 2011;71:5904-5914.
54. Beauchamp EM, Ringer L, Bulut G, et al. Arsenic trioxide inhibits human cancer cell growth and tumor development in mice by blocking Hedgehog/GLI pathway. *J Clin Invest.* 2011;4:148-160.
55. Lauth M, Rohnalter V, Bergstrom A, Kooshesh M., Svenningsson P, Toftgard R Antipsychotic drugs regulate hedgehog signaling by modulation of 7-dehydrocholesterol reductase levels. *Mol Pharmacol.* 2010;78:486-496.
56. Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell.* 2010;17:388-399.
57. Rudin CM, Jimeno A, Miller WH, et al. A phase I study of IPI-926, a novel hedgehog pathway inhibitor, in patients (pts) with advanced or metastatic solid tumors [abstract]. *J Clin Oncol.* 2011;29(suppl). Abstract 3014.