More than 3.5 million skin cancers are diagnosed in more than two million Americans annually, making it the most common form of cancer in this country. Basal cell carcinoma (BCC) is the most common cancer in the United States with an estimated annual incidence of 0.5%.\(^1\)\(^2\) BCC is generally thought to affect men and women equally. Overall, the age-adjusted incidence of basal cell carcinoma per 100,000 persons was 25.9 for women and 20.9 for men; however, one analysis shows the incidence of BCC has increased significantly among women only.\(^3\) Compared to squamous cell carcinoma (SCC), BCC is more common on areas of only moderate exposure, e.g. upper trunk in men and women and lower legs in women.\(^4\) Yet, up to 85 percent of BCCs occur in the sun-exposed head and neck region.\(^5\) Several studies have illustrated the link between UV exposure and BCC to be weaker than the link between UV exposure and AK or squamous cell carcinoma.\(^6\)

**Pathogenesis**

Elucidating the pathogenesis of basal cell nevus syndrome (BCNS), also known as Gorlin’s syndrome, has greatly enhanced our understanding of the pathogenesis of BCC. This genetic syndrome is inherited as an autosomal dominant trait and is typically expressed in young adulthood with patients presenting with multiple basal cell cancers. Mutation of the tumor suppressor gene PTCH, which is located on chromosome 9 q22-q31, has been implicated in 40 to 80 percent of cases of BCNS.\(^7\) The PTCH gene product functions as a transmembrane receptor for the Sonic hedgehog protein (SHH) (which normally acts to inhibit another transmembrane protein Smoothened (SMO)), leading to aberrant cell proliferation.

**Key Points**

Basal cell carcinoma (BCC) is the most common cancer in the US. PTCH gene mutations have now been implicated in both sporadic and hereditary forms of BCC. The PTCH gene functions as a transmembrane receptor for the Sonic hedgehog protein (SHH) which normally acts to inhibit another transmembrane protein Smoothened (SMO), leading to aberrant cell proliferation.

BCC generally is a slowly progressing, locally invasive malignancy with a low rate of metastasis (0.0028 to 0.5%). Generalized dissemination of BCC is very rare (<0.1%), but cases of metastasis to the lymph nodes, lung, bone, and liver have been described. Some experts suggest current data may underestimate the incidence of metastatic BCC.

Most local BCCs are treated with surgical excision, though scarring, tissue loss, and pigmentation changes are possible. Other available treatments include destruction, photodynamic therapy (PDT), imiquimod cream, and 5-fluorouracil. Investigational agents for localized BCC include ingenol mebutate (PEP005) and celecoxib. Vismodegib (GDC-0449) has been submitted to the FDA for treatment of advanced BCC. Oral alpha-difluoromethylornithine (DFMO) is under investigation as a preventive agent.
mutations have now been implicated in both sporadic and hereditary forms of BCC.8

Although BCC is felt to originate from mutation of the basal epithelial cell, there is evidence to suggest that it may also originate from actinic keratoses (AKs), common dysplastic keratinocytic epidermal lesions caused by chronic ultraviolet light (UV) exposure.9 AKs primarily affect fair skinned, middle-aged people, and have a reported prevalence of up to 60 percent in individuals over 60 years of age.10 Historically, AK was classified as a pre-malignant lesion; in recent years it has been determined that AKs are part of a spectrum of disease progression, ranging from sun-damaged skin to squamous cell carcinoma in situ (SCC).11-13 Despite the common belief that AKs evolve only into SCC, in one large study, BCC was shown to evolve from lesions previously diagnosed as AK. There was a one year risk of evolution of 0.48% and a four year risk of 1.56% (compared to 0.60% and 2.57% for SCC, respectively).14

Clinical Presentation

BCC generally is a slowly progressing, locally invasive malignancy with a low rate of metastasis (0.0028 to 0.5%).15 Clinically, BCC classically presents as a pearly papulonodular lesion with rolled borders and telangiectasias with or without ulceration in fair skinned individuals in the fourth decade of life and beyond. Untreated lesions may remain little changed over many years16 or may advance locally, developing ulcerations and crusting. There are several clinical and histological variants,17,18 which occur with variable frequency. Among the most commonly seen variants are:

a.) Morpheaform or sclerotic BCC, which can present as white-to-yellow macules;
b.) Basosquamous variant, which is often ulcerated and crusted;
c.) Pigmented BCC, which may clinically appear similar to a melanoma.

BCC can grow aggressively, causing extensive local tissue damage. More generalized dissemination of BCC is also very rare (<0.1%), but cases of metastasis to the lymph nodes, lung, bone, and liver have been described.14 Clinical features strongly associated with aggressive BCC phenotype include larger size (greater than 3.0 cm diameter), facial location (midface or ear), long duration of presence, incomplete excision, perineural or perivascular invasion, and histologic variants such as morpheaform BCC, infiltrating BCC, and basosquamous BCC.14 Of note, some experts suggest current data may underestimate the incidence of metastatic BCC.21 Mortality rates associated with BCC are low.

Histology

Histologically, BCC is composed of proliferation keratinocytes from the basal cells of the epidermis. Immunohistochemical studies have defined BCC as a malignant tumor of follicular germinative cells.22 Nodular and superficial BCC tend to be less aggressive histologically, with aggregates of basophilic cells with palisading peripheral cells and little to no mitotic activity. The surrounding stroma may show retraction and fibrosis, and there may be calcification and mucin centrally. More aggressive types—morpheaform, infiltrating, and basosquamous—have distinct histologic features. Morpheaform or sclerosing BCC shows thin, elongated and angular, poorly circumscribed tumor islands with limited peripheral palisading. They often invade subcuto- cutaneously and are often found in a dense and sclerotic dermis. Infiltrating BCC are also poorly circumscribed, with tumor strands that may invade deep beyond the dermis. Basosquamous variant, which represents a squamousized BCC, shows squamotized cells superficially, usually beneath an ulcer, with more typical basaloid cells deeper. However, a true basosquamous carcinoma is a collision tumor between BCC and SCC.23

Available Treatments

Local BCC. Most local BCCs are treated with surgical excision, though scarring, tissue loss, and pigmentation changes are commonly associated with this procedure. The risk for recurrence associated with surgical and
destructive modalities is clinically low. Studies suggest the rate of recurrence following surgical excision of head and neck lesions ranges from about 3.5 percent—^2.23—even when staged excision is performed—up to 8.2 percent.27 Recently, a study comparing the recurrence rates of non-melanoma skin cancer was conducted at the VA hospital and showed comparable recurrence rates for electrodesication and curettage (ED&C, 1.6%) as compared to excision (4.2%) and Mohs (3.5%). Median time to recurrence was 1.5 years, 3.8 years, and six years, respectively.28 A high percentage of tumors treated by ED&C were located on the trunk and extremities. While a selection bias may play a factor here, low rates of recurrence following ED&C have been previously reported.29

**Local and/or Locally Advanced BCC.** Photodynamic therapy (PDT) and imiquimod cream represent alternative treatment options often prescribed because they offer a low risk of scarring in conjunction with good cosmesis and high sustained histologic clearance rates.30-32 Data indicate that the complete response of BCC to PDT is 62 percent; response was better for superficial BCC (82 percent) than for nodular BCC (33 percent).33 A similar overall response rate (64 percent) was found for PDT in the management of either BCC or SCC.34 Guidelines outside the US support the use of PDT for certain instances of BCC.35

Topical therapies such as imiquimod or 5-fluorouracil alone have also demonstrated impressive results. Among 82 patients with superficial BCC on various anatomical locations, application of imiquimod 5% three times a week for four weeks provided clinical clearance rates of 89 percent and 85 percent, respectively, at one and two years.37 An analysis of published data found that imiquimod had clearance rates of 43 percent to 100 percent for superficial BCC, 42 percent to 100 percent for nodular BCC, and 56 percent to 63 percent for infiltrative BCC. Fluorouracil had clearance rates of 90 percent for superficial BCC.38

**Investigational Treatments**

**Local BCC.** Recently, a novel agent called ingenol mebutate (PEP005) was demonstrated in phase III studies to be a promising therapeutic option for superficial basal tumors in addition to actinic keratoses.39 One Australian study showed a favorable safety profile for two applications of PEP005 gel at concentrations of 0.0025%, 0.01%, or 0.05% given either on consecutive days or dosed one week apart for BCC. The most convincing results were reflected in the histological clearance rate of 63 percent of those randomized to the 0.05% treatment arm as compared to controls. The incidence of adverse events was low and included flaking, scaling, dryness, erythema extending beyond the application site, application-site pain, and headache in several subjects in this small study.37

Also under investigation for the treatment BCC is celecoxib. In a three-year, double-blind, randomized clinical trial in 60 (PTCH1(+/-)) patients with basal cell nevus syndrome, researchers detected a trend for oral celecoxib to decrease BCC burden in all subjects. Reduction of new lesions was most significant among patients with less severe disease, defined as fewer than 15 BCCs at study entry. Treated patients had a 20 percent annual increase in BCCs compared to 50 percent for controls.40

**Advanced BCC.** As noted above, PTCH mutations leading to errant SHH signaling were first implicated in BCC development in the 1990s.4 Activation of the SHH pathway has been associated with the development of a number of human malignancies, with BCC being the most extensively investigated and best characterized.41 Ordinarily inactive in adults, the hedgehog pathway...
promising. A phase I trial of the orally active, selective hedgehog pathway in the treatment of BCCs have been but recently trials with a small molecule inhibitor of the pharmacological implications. Best illustrated in nevoid basal cell syndrome, and has signaling and unrestrained proliferation of basal cells. This is illustrated in nevoid basal cell syndrome, and has pathological implications.

Early findings had limited clinical utility for physicians but recently trials with a small molecule inhibitor of the hedgehog pathway in the treatment of BCCs have been promising. A phase I trial of the orally active, selective hedgehog inhibitor vismodegib (GDC-0449) involved patients with solid tumors, including BCC, refractory to current therapies or for which no standard therapy existed. Thirty-three of 68 patients had advanced basal cell carcinoma (BCC), eight had pancreatic cancer, and one had medulloblastoma; 17 other types of cancer were also represented. Tumor responses were observed in 20 patients (19 with BCC and one unconfirmed response in medulloblastoma), 14 patients had stable disease as best response.

In another recent phase I study, 33 subjects with metastatic or locally advanced BCC were randomized to receive oral vismodegib 150mg/day (17 patients), 270mg/day (15 patients), and 540mg/day (one patient) for a median duration of 9.8 months. Of the 33 subjects enrolled, 18 had an objective response to the selective hedgehog inhibitor, two with a complete response and 16 with a partial response. Recently presented data show that vismodegib-treated patients developed on average 0.7 BCCs per month compared to 1.74 BCCs per month in untreated controls. The size of existing lesions decreased in the treatment group. The trial was halted due to the disparity in response, with untreated subjects faring poorly compared to those on treatment. Observed adverse effects of treatment include fatigue, hyponatremia, muscle spasm, atrial fibrillation, loss of taste, muscle cramps, and hair thinning.

ERVANCE BCC is an international, single-arm, multicenter, two cohort, open-label phase II study with 104 patients with locally advanced or metastatic BCC who were given 150mg vismodegib orally daily until disease progression or intolerable toxicity. Primary endpoint was defined as an objective response rate by independent review, and secondary endpoints included objective response rate by investigator, progression-free survival, duration of response, and absence of residual BCC in patients with locally advanced BCC. Forty-three percent of patients with locally advanced BCC and 30 percent of patients with metastatic BCC showed an overall response rate. Median duration of progression-free survival was 9.5 months. Side effects were similar to those seen in the phase I trials, and included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite and diarrhea.

Prevention. In clinical studies, oral alpha-difluoromethylornithine (DFMO) 500mg/m²/day was safe and well tolerated, significantly inhibiting phorbol ester-induced skin ODC activity and thus formation of new NMSC in patients with a history of skin cancer. In all, 299 patients were randomized to oral DFMO or placebo. Despite a lack of significant difference in total NMSCs between treated patients and controls, there was a statistically significant difference in the number of new BCCs observed among treated patients.

Conclusion

Though there are clearly more options now for BCC treatment than have been available in the past, treatment continues to remain a challenge. BCC is generally a slow growing tumor with superficial invasion, but clinically aggressive variants do occur and can be associated with significant morbidity and even mortality. Surgery remains the first line treatment, but there are options available and under investigation for inoperable, locally advanced or metastatic BCC that have expanded the treatment armamentarium from even a year ago.

Drs. Frankel and Goldenberg have no conflicts of interest to report.


