melanoma recommend a comprehensive history and physical examination every 6–12 months for 5 years, and then annually as clinically indicated. Particular attention should be paid to the draining lymph nodes in stage I–III patients as resection of lymph node recurrences may still be curative. A CBC, LDH, and chest x-ray are recommended at the physician's discretion, but are ineffective tools for the detection of occult metastases. Routine imaging for metastatic disease is not recommended at this time. For patients with higher stage disease (IIB–IV), imaging (chest x-ray, CT, and/or PET/CT scans) every 4–12 months can be considered. Because no discernible survival benefit has been demonstrated for routine surveillance, it is reasonable to perform scans only if clinically indicated.

NONMELANOMA SKIN CANCER

Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States. Although tumor registries do not routinely gather data on the incidence of basal cell and squamous cell skin cancers, it is estimated that the annual incidence is 1.5–2 million cases in the United States. Basal cell carcinomas (BCCs) account for 70–80% of NMSCs. Squamous cell carcinomas (SCCs), which comprise ~20% of NMSCs, are more significant because of their ability to metastasize and account for 2400 NMSC deaths annually. There has also been an increase in the incidence of nonepithelial skin cancer, especially Merkel cell carcinoma, with nearly 5000 new diagnoses and 3000 deaths annually.

PATHOPHYSIOLOGY AND ETIOLOGY

The most significant cause of BCC and SCC is UV exposure, whether through direct exposure to sunlight or by artificial UV light sources (tanning beds). Both UVA and UVB can induce DNA damage through free radical formation (UVA) or induction of pyrimidine dimers (UVB). The sun emits energy across the UV spectrum, whereas tanning bed equipment typically emits 97% UVA and 3% UVB. DNA damage induced by UV irradiation can result in cell death or repair of damaged DNA by nucleotide excision repair (NER). Inherited disorders of NER, such as xeroderma pigmentosum, are associated with a greatly increased incidence of skin cancer and help to establish the link between UV-induced DNA damage, inadequate DNA repair, and skin cancer. The genes damaged most commonly by UV in BCC involve the Hedgehog pathway (Hh). In SCC, *p53* and *N-RAS* are commonly affected. There is a dose-response relationship between tanning bed use and the incidence of skin cancer. As few as four tanning bed visits per year confers a 15% increase in BCC and an 11% increase in SCC and melanoma. Tanning bed use as a teenager or young adult confers greater risk than comparable exposure in older individuals. Other associations include blond or red hair, blue or green eyes, a tendency to sunburn easily, and an outdoor occupation. The incidence of NMSC increases with decreasing latitude. Most tumors develop on sun-exposed areas of the head and neck. The risk of lip or oral SCC is increased with cigarette smoking. Human papillomaviruses and UV radiation may act as cocarcinogens.

Solid organ transplant recipients on chronic immunosuppression have a 65-fold increase in SCC and a 10-fold increase in BCC. The frequency of skin cancer is proportional to the level and duration of immunosuppression and the extent of sun exposure before and after transplantation. SCCs in this population also demonstrate higher rates of local recurrence, metastasis, and mortality. There is increasing use of tumor necrosis factor (TNF) antagonists to treat inflammatory bowel disease and autoimmune disorders such as rheumatoid and psoriatic arthritis. TNF antagonists may also confer an increased risk of NMSC. BRAF-targeted therapy can induce SCCs including keratoacanthoma-type SCCs in keratinocytes, with preexisting *H-RAS* overexpression present in approximately 60% of patients.

Other risk factors include HIV infection, ionizing radiation, thermal burn scars, and chronic ulcerations. Albinism, xeroderma pigmentosum, Muir-Torre syndrome, Rombo's syndrome, Bazex-Dupré-Christol syndrome, dyskeratosis congenita, and basal cell nevus syndrome (Gorlin syndrome) also increase the incidence of NMSC. Mutations in Hh genes encoding the tumor-suppressor patched homolog 1 (*PTCH1*) and smoothened homolog (*SMO*) occur in BCC. Aberrant *PTCH1* signaling is propagated by the nuclear transcription factors Gli1 and Gli2, which are salient in the development of BCC and have led to the FDA approval of an oral SMO inhibitor, vismodegib, to treat advanced inoperable or metastatic BCC (Fig. 105-4). Vismodegib also reduces the incidence of BCC in patients with basal cell nevus syndrome who have *PTCH1* mutations, affirming the importance of Hh in the onset of BCC.

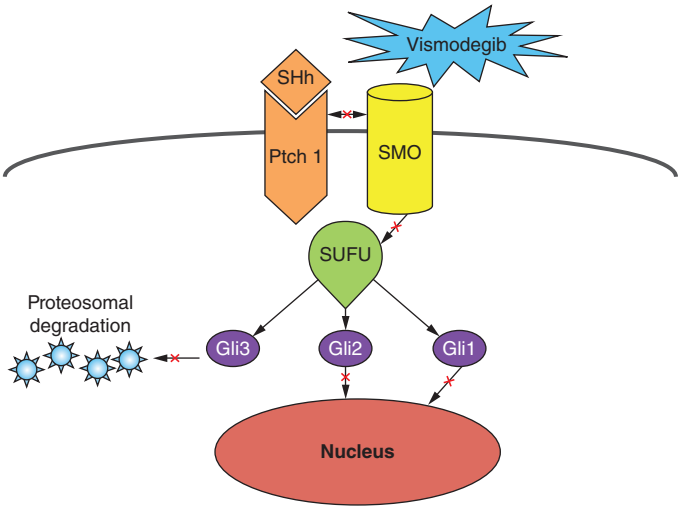

FIGURE 105-4 Influence of vismodegib on the hedgehog (Hh) pathway. Normally, one of three Hh ligands (sonic [SHh], Indian, or desert) binds to patched homolog 1 (PTCH1), causing its degradation and release of smoothened homolog (SMO). The downstream events of SMO release are the activation of Gli1, Gli2, and Gli3 through the transcriptional regulator known as SUFU. Gli1 and Gli2 translocate to the nucleus and promote gene transcription. Vismodegib is an SMO antagonist that decreases the interaction between SMO and PTCH1, resulting in decreased Hh pathway signaling, gene transcription, and cell division. The downstream Hh pathway events inhibited by vismodegib are indicated in red.

CLINICAL PRESENTATION

Basal Cell Carcinoma BCC arises from epidermal basal cells. The least invasive of BCC subtypes, superficial BCC, consists of often subtle, erythematous scaling plaques that slowly enlarge and are most commonly seen on the trunk and proximal extremities (Fig. 105-5). This BCC subtype may be confused with benign inflammatory dermatoses, especially nummular eczema and psoriasis. BCC also can present as a small, slowly growing pearly nodule, often with tortuous telangiectatic vessels on its surface, rolled borders, and a central crust (nodular BCC). The occasional presence of melanin in this variant of nodular BCC (pigmented BCC) may lead to confusion with melanoma. Morpheaform (fibrosing), infiltrative, and micronodular BCC, the most invasive and potentially aggressive subtypes, manifest as solitary, flat or slightly depressed, indurated whitish, yellowish, or pink scar-like plaques. Borders are typically indistinct, and lesions can be subtle; thus, delay in treatment is common, and tumors can be more extensive than expected clinically.

Squamous Cell Carcinoma Primary *cutaneous SCC* is a malignant neoplasm of keratinizing epidermal cells. SCC has a variable clinical course, ranging from indolent to rapid growth kinetics, with the potential for metastasis to regional and distant sites. Commonly, SCC appears as an ulcerated erythematous nodule or superficial erosion on sun-exposed skin of the head, neck, trunk, and extremities (Fig. 105-5). It may also appear as a banal, firm, dome-shaped papule or rough-textured plaque. It is commonly mistaken for a wart or callous when the inflammatory response to the lesion is minimal. Clinically visible overlying telangiectasias are uncommon, although dotted or coiled vessels are a hallmark of SCC when viewed through a dermatoscope.