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Basal Cell Nevus Syndrome

A Brave New World

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

A 53-year-old man with basal cell nevus syndrome sought a different treatment modality than surgical excisions for his numerous basal cell carcinomas. He was referred to a clinical trial involving an oral antagonist of the *PTCH* signaling pathway. The results were promising.

REPORT OF A CASE

A 53-year-old man had been treated for basal cell nevus syndrome (BCNS, or Gorlin syndrome) for over 30 years. At least 750 basal cell carcinomas (BCCs), including sclerosing and perineural tumors, had been surgically removed from his face, chest, back, arms, and legs. He first presented with BCC skin cancers in his early 20s. The patient had several other features of BCNS, including palmar pits, partial cleft lip, bifid ribs, frontal bossing, marked pectus deformity, and odontogenic jaw cysts. Previous surgical procedures to treat jaw cysts resulted in speech difficulty. He also had thyroid nodules, which on fine-needle aspiration were found to be benign mixed cystic nodules.

In February 2003, the patient developed a deep-seated nodule in the right superior inguinal groin. The tumor was a metastatic BCC to the lymph node, although no primary tumor was identified on the right leg or in the vicinity of the affected lymph node. Only 1 of 8 lymph nodes excised was positive for BCC with extracapsular spread of the tumor. He successfully underwent surgical node dissection and excision with subsequent radiation therapy to the site. He has persistent lymphedema of the right leg but no nodal recurrence or other organ involvement. To date, he has not developed BCCs at the site of the prior radiation therapy.

The patient's mother, sister, and 2 brothers also have BCNS; 1 brother was diagnosed as having a medulloblastoma. His fraternal twin brother was treated for numerous BCCs and died of mucinous cell carcinoma of the oral mucosa that metastasized to the neck and lungs. At the time of writing, the patient had become reluctant to undergo further surgical procedures to treat BCCs and the periods between operations became increasingly longer. As a result, he had numerous tumors and extensive, large tumors of the face, neck, and back.

THERAPEUTIC CHALLENGE

From January 25, 1996, to July 11, 2008, the patient had undergone Mohs micrographic surgery and surgical excisions for 282 histologically confirmed BCCs. He also completed several courses of treatment with imiquimod cream, fluorouracil cream, 5%, and oral retinoids[1] with marginal therapeutic benefit. He had been part of an experimental study involving the pulsed-dye laser (595-nm wavelength) for superficial BCC.[2] Surgery was the only modality to successfully eliminate his BCCs. Most recently he had developed a number of larger BCCs that would have required large, debilitating, and possibly deforming operations. He was averse to undergo these procedures, and delayed visits for surgical treatment, unless the tumors were bleeding, ulcerating, or cosmetically undesirable.

SOLUTION

We sought a completely different treatment modality to treat his tumors. He was referred for evaluation and treatment to TGen Clinical Research Services at Scottsdale Healthcare in Scottsdale, Arizona.[3] A novel therapeutic agent, GDC-0449 [2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]phenyl)-4-(methylsulfonyl)benzamide], is a small molecule inhibitor of the Hedgehog signaling pathway via interaction with smoothened, a 7-transmembrane G-protein receptor. GDC-0449 was developed by Genentech (San Francisco, California) and was jointly validated through a series of preclinical studies performed under a collaborative agreement between Genentech and Curis (Cambridge, Massachusetts). It is currently being evaluated in an ongoing phase 1 clinical trial and pivotal phase 2 trial for advanced BCC. A medulloblastoma trial is also ongoing under the National Cancer Institute Cooperative Research and Development Agreements (NCI CRADA). GDC-0449 has demonstrated favorable pharmacodynamic and pharmacokinetic properties in the phase 1 clinical trial. Reportable adverse effects included 2 cases of reversible hyponatremia, 1 case of drug-related fatigue, and mild hair loss in some patients.[4]

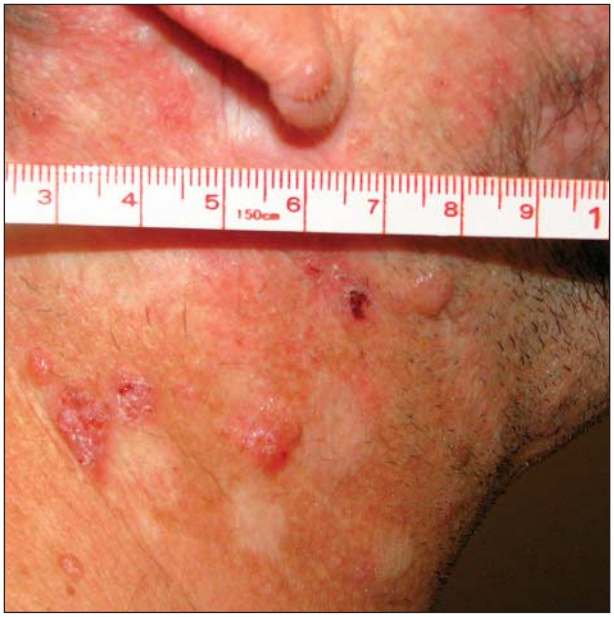

Figure 1. Numerous basal cell carcinomas, evidenced by erythematous patches and plaques, some with ulceration, on the patient's neck and lower cheek prior to treatment with GDC-0449 [2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]phenyl)-4-(methylsulfonyl)benzamide].

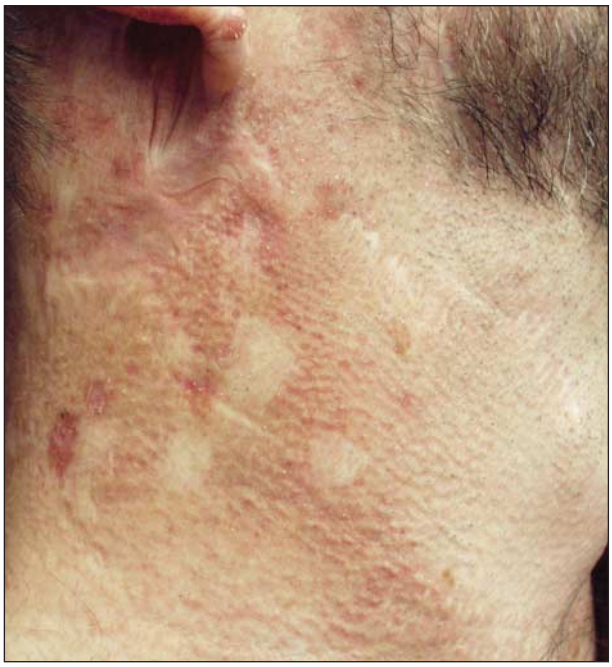

Figure 2. Thinning and resolution of several erythematous patches and plaques on the patient's neck and cheek 12 weeks after beginning treatment with GDC-0449 [2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]phenyl)-4-(methylsulfonyl)benzamide].

The patient started oral therapy with GDC-0449, 270 mg/d, in August 2008; after 8 weeks he noted considerable reduction in the number and size of his BCCs. Clinical examination after 12 weeks revealed no additional BCCs on his skin, and most of his existing BCCs had clinically regressed (**Figures 1**, **2**, **3**, and **4**). After 18 weeks of oral therapy, several of his BCCs had clinically resolved. The erythema that had covered his face had also disappeared. He had no notable symptoms secondary to the medication on review of systems, and a physical examination was unremarkable except for hair thinning of the scalp vertex. Six months after starting therapy his BCCs had disappeared, except for one 8-mm-diameter lesion on the concha bowl. The frontal thinning of the hair had progressed to almost complete frontal alopecia and included his eyebrows and eyelashes.

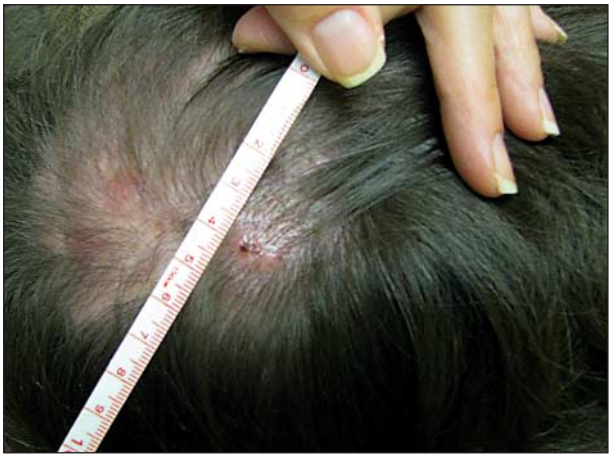

Figure 3. One large ulcerated basal cell carcinoma on the scalp vertex, in addition to a few erythematous patches on the anterior scalp, prior to treatment with GDC-0449 [2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]phenyl)-4-(methylsulfonyl)benzamide].

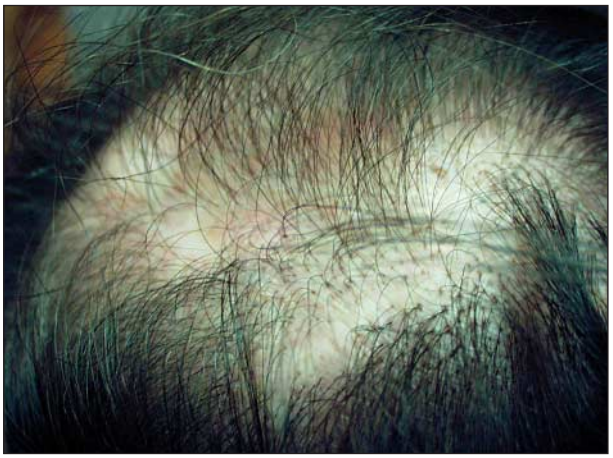

Figure 4. Resolution of crusted plaque and erythematous patches on the scalp 12 weeks after beginning treatment with GDC-0449 [2-chloro-*N*-(4-chloro-3-[pyridin-2-yl]phenyl)-4-(methylsulfonyl)benzamide]. Note diffuse hair thinning after treatment when compared with pretreatment photographs in Figure 3 (the hair thinning does not bother our patient).

COMMENT

Basal cell nevus syndrome, or Gorlin syndrome, is the most common inherited syndrome associated with BCCs.[5] This autosomal dominant disorder is diagnosed with 2 major criteria or 1 major and 2 minor criteria.[6] The major criteria include (1) more than 2 BCCs or 1 BCC in patients younger than 20 years; (2) odontogenic keratocysts of the jaw (proven by histologic analysis); (3) 3 or more palmar or plantar pits; (4) bilamellar calcification of the falx cerebri; (5) bifid, fused, or markedly splayed ribs; and (6) a first-degree relative with NBCCS. The minor criteria include (1) macrocephaly; (2) congenital malformations, such as cleft lip or palate, frontal

bossing, coarse facies, and moderate or severe hypertelorism; (3) other skeletal abnormalities, such as Sprengel deformity, marked pectus deformity, and marked syndactyly of the digits; (4) radiologic abnormalities, such as bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet; and (5) ovarian fibroma or medulloblastoma.[5,6] The incidence of BCNS is estimated to be 1 in 50 000 to 150 000 in the general population.

Our patient had a family history of basal cell nevus syndrome; his twin brother, mother, and other siblings all had the disease. During his entire life, he had had tumors that were too numerous to count. He has considerable cosmetic disfigurement both from the tumors and the resulting operations of his face and body, with considerable psychological effects. He has not had an easy life, especially because of multiple procedures and physician visits. His speech is impaired owing to numerous procedures to treat jaw cysts.

Patients with BCNS have a germline mutation in the *PTCH* gene (OMIM *601309), a tumor suppressor gene and the human homologue of the Drosophila patched gene, 35 kb in length and consisting of 23 exons.[3] *PTCH* encodes a receptor, consisting of 2 large extracellular loops and 12 transmembrane domains, that binds and acts in opposition to the sonic hedgehog ligand, a member of the hedgehog signaling family. When functioning normally, *PTCH* inhibits smoothened, causing tumor suppression. When mutated, *PTCH* is unable to inhibit smoothened, which leads to nuclear transcription and tumor proliferation. Mutations in *PTCH* have also been found in sporadic BCCs.[6,7] Until now, there have been no effective treatments for BCNS, and some patients die from metastatic BCCs or other solid organ tumors such as medulloblastoma. Radiation therapy in these patients is used with extreme caution owing to an increased risk of developing BCCs at irradiated sites.

Using the words of our patient, this new class of medication has dramatically changed and improved his entire life. In a preliminary report in abstract form,[8,9] GDC-0449 has had documented activity in patients with metastatic or locally advanced BCC. This treatment has the potential to change the significance and prognosis of BCC, especially in patients with BCNS. What is now a surgical disease may become a medically treatable disease. At this point, the results are limited and preliminary, and complete data regarding safety and efficacy are not yet available. A major limitation is that skin biopsies were not performed to assess tumor clearance pretreatment or posttreatment; only a skin biopsy could definitively confirm histologic clearance. Moreover, photographs to assess tumor size were not performed with uniform poses or lighting. This type of data, collected through controlled clinical trials comprising several patients, will obviously have an impact on the use of this drug in the future.

The gene most often altered in sporadic BCCs is the *PTCH* gene followed by point mutations in the *p53* tumor suppressor gene and mutations in the oncogene *CDKN2A*.[3] Although this novel drug specifically targets the Hedgehog signaling pathway, not all BCCs may respond to such treatment owing to different mutations involved in tumor development, growth, and metastasis. The question that remains is, will an oral medication be able to successfully treat cutaneous BCCs in the future? Will an oral medication be capable of eradicating other types of tumors in the future? This therapeutic modality is a promising development in the treatment of BCNS and possibly even sporadic BCCs.

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