

Hedgehog Pathway Inhibitor Helps Fight Cancer

BY MARY ANN MOON

A new drug that inhibits the hedgehog signaling pathway has shown “remarkable” antitumor activity against basal cell carcinoma and medulloblastoma, according to two reports.

The hedgehog signaling pathway regulates cell growth and differentiation during early development but is inactive in healthy adults. However, it appears

that mutations in components of the pathway can cause malignant growth in some cases of medulloblastoma, the most common brain cancer in children, and in several cancers in adults, notably basal cell carcinoma.

The hedgehog pathway derived its name from its signaling molecule, a polypeptide ligand called Hedgehog [Hh] because the mutation it caused when it was first discovered in fruit flies pro-

duced stubby, hairy-looking larvae resembling hedgehogs.

The new oral agent, GDC-0449, was developed to selectively and potentially inhibit hedgehog signaling without producing the adverse effects common with conventional chemotherapy. It appears to have done so in a phase I clinical trial of patients with advanced or metastatic basal cell carcinoma and in a single case study testing it against medulloblastoma

refractory to all other treatments. Both studies were supported by Genentech Inc., developer of GDC-0449.

These results indicate that targeting the hedgehog signaling pathway may be a promising avenue for a whole new class of cancer therapies, Dr. Andrzej A. Dlugosz and Dr. Moshe Talpaz of the University of Michigan, Ann Arbor, said in an editorial comment accompanying the two reports.

“Although the total number of patients with advanced or metastatic basal cell carcinoma is small, these studies should ignite renewed interest in testing hedgehog pathway inhibitors in patients with typical basal cell carcinoma” as well as other cancers, they said.

“For patients at especially high risk for multiple basal cell tumors, an effective medical treatment would be a welcome alternative to repeated surgical proce-

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dures, which can be especially disfiguring when the tumors occur on the face,” Dr. Dlugosz and Dr. Talpaz said (N. Engl. J. Med. 2009 [doi 10.1056/NEJM e0906092]).

Alternatively, tumor debulking with the use of hedgehog inhibitors, followed by surgical excision, might prove beneficial in many patients, they added.

In the clinical trial, Dr. Daniel D. Von Hoff of the Translational Genomics Research Institute in Scottsdale, Ariz., and his associates assessed GDC-0449 in 18 patients with metastatic and 15 patients with locally advanced basal cell carcinoma that had been refractory to surgery, radiotherapy, and chemotherapy.

A total of 18 patients showed a clinical response, 11 showed stable disease for up to 10 months, and 4 had disease progression, Dr. Von Hoff and his colleagues reported (N. Engl. J. Med. 2009 [doi.10.1056/NEJMoa0905360]).

The overall response rate was 55%. Dr. Dlugosz and Dr. Talpaz termed the 50% response rate among patients with metastatic disease “remarkable.”

There were no dose-limiting toxic effects or grade-5 adverse events during the study. One grade-4 event occurred (asymptomatic hyponatremia) and several patients reported a variety of problems that may or may not have been related to treatment, such as fatigue and weight loss. Only one patient discontinued treatment after 8 months, citing abdominal pain, fatigue, weight loss, anorexia, and dysgeusia.

In the case study, Dr. Charles M. Rudin of Johns Hopkins University, Baltimore, and his associates assessed GDC-0449 in a 26-year-old man with a 4-year history

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AEIOU May Help Make Merkel Cell Diagnosis

BY DOUG BRUNK

PORTLAND, ORE. — Skin lesions are a hallmark of Merkel cell carcinoma, yet dermatologists often find themselves out of the loop in diagnosing patients with the disease, said Dr. Paul Nghiem.

“These [lesions] are typically biopsied as a cyst and the patient usually has to argue for one, two, or three doctor’s visits to have the lesion biopsied,” Dr. Nghiem said at the annual meeting of the Pacific Dermatologic Association. “They’re usually biopsied by a reluctant primary care physician who thinks they’re taking off a cyst. Then they may be referred to medical oncology or to surgical oncology, but rarely to dermatology.”

About 1,500 new cases of Merkel cell carcinoma (MCC) are diagnosed in the United States each year (J. Invest. Dermatol. 2007;127:2100-3), which is about the same incidence as cutaneous T-cell lymphoma or dermatofibrosarcoma protuberans, said Dr. Nghiem, an expert on the disease who is associate professor of dermatology, medicine, and pathology at the University of Washington, Seattle.

MCC is significantly more lethal than melanoma (40% vs. 15%, respectively), and its reported incidence has increased threefold since 1986 (J. Surg. Oncol. 2005;89:1-4).

“A big reason for that is that it’s not missed as much,” Dr. Nghiem said. “There are better tools for pathologists to use to make the diagnosis.”

The three main risk factors for MCC are prolonged sun exposure, immune suppression, and age over 50 years. “Ninety-four percent of all MCC cases are in people aged 50 or older,” he said. “There is a very strong synergy with age” (J. Am. Acad. Dermatol. 2008;58:375-81).

Dr. Nghiem said that HIV-positive patients had about a 13-fold increase of MCC in one study (Lancet 2002;359:497-8), while another study showed that solid organ transplant recipients have about a 10-fold increase (Transplantation 1999;68:1717-21).

He and his associates devised the acronym AEIOU to describe the clinical features of Merkel cell carcinoma based on an analysis of 195 patients given the diagnosis between 1980 and 2007 (J. Am. Acad. Dermatol. 2008; 58:375-81). The acronym stands for Asymptomatic, Ex-

panding rapidly, Immune compromised, Older than 50, and UV-exposed, fair skin.

“Under no circumstances do I think that this is a highly specific test,” said Dr. Nghiem, whose clinic is based at the Fred Hutchinson Cancer Research Center in Seattle. “It’s not going to be up there with the ABCDs of melanoma, but if you see these characteristics together, you may want to think about doing a biopsy.”

More than half of the lesions in the 195 patients evaluated (56%) were presumed to be benign at biopsy, and 32% presented on the head and neck, followed by the lower limb (30%), upper limb (20%), trunk (10%), and buttock (8%).

The majority of lesions (81%) presented on sun-exposed skin, but one in six was in a sun-protected site.

Nearly all of the lesions (88%) were asymptomatic (“neither tender nor itchy,” he said), 63% doubled in size in the past 3 months, and 8% of the patients were profoundly immune suppressed. “That is a 16-fold increase over the normal population, but still a minority of all Merkel cell cases,” he said, noting that 90% of the patients studied were at least 50 years of age and that 98% were fair skinned.

“Taken together, 89% of all Merkel cell carcinomas had three or more of these clinical AEIOU features,” he said.

Optimal therapy for MCC is unique among skin cancers, he said, in that sentinel lymph node biopsy (SLNB) is usually indicated and the disease is “exquisitely sensitive” to radiation.



The majority of Merkel cell carcinoma lesions appear on sun-exposed skin, but one in six has been found to appear on sun-protected areas.



Merkel cell carcinoma has a significantly higher mortality rate, compared with melanoma, and reported incidence has increased threefold since 1986.

“If I had one modality to treat MCC, it would be radiation,” he said.

SLNB is important for prognosis, he added, because it “results in more accurate staging and has therapeutic implications. If it’s microscopically positive [the cancer] will very likely develop in that node bed within a few months if you don’t do anything.”

In Dr. Nghiem’s opinion, the best local therapy for MCC is pathologically clear margins when the primary tumor is less than 1 cm, there is no lymphovascular invasion, there is no profound immune suppression, and the SLNB is negative.

“If all of those things are kosher, you are pretty much okay with a negative margin incision,” he said. “Otherwise, adjuvant radiation is very helpful.”

He described the current staging system for MCC as “a mess.” Five staging systems are currently being used, he said, yet all of them are based on studies of fewer than 300 patients and none has been validated.

MCC staging by the American Joint Committee on Cancer is currently performed using the same

staging system as for 82 other non-melanoma skin cancers, including basal cell carcinoma, squamous cell carcinoma, and adnexal neoplasms.

The key histologic feature of MCC is a perinuclear dot pattern of cytokeratin-20, “which is the rule, not the exception,” he said.

Dr. Nghiem finds MCC treatment guidelines from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology to be especially useful. The guidelines are updated annually and are available at www.nccn.org.

MCC typically is coded as ICD-9 code 173 (other malignant neoplasm of skin). “Unfortunately, this means that MCC costs can’t be tracked at all and, more importantly, patients are denied care,” he said. Things should improve on that front shortly, however. Dr. Nghiem said that the CDC is expected to release eight new diagnostic codes specific for MCC this month.

Little is known about MCC biology, but a study from 2008 found that a new polyomavirus is present in the vast majority of cases (Science 2008;319:1096-100). “This is only the sixth example of a virus clearly linked to human cancer,” Dr. Nghiem said.

He disclosed that he has received funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the American Cancer Society. ■

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of medulloblastoma. The patient had undergone gross total resection of the tumor, craniospinal irradiation, extensive chemotherapy, autologous stem-cell transplantation, and additional systemic treatment with temozolomide and bevacizumab, but nevertheless had widespread skeletal and soft tissue metastases. With no alternative therapies left, he was offered CDC-0449.

Within 1 month, supraclavicular lymphadenopathy resolved, sternal masses regressed, and the patient reported that his intractable pain had resolved. After a

few more weeks, more nodules regressed and the patient had returned to a normal level of activity. After a few more weeks, further metastases were markedly diminished or, in the case of a disabling epidural mass at C7, no longer detectable.

After 3 months of treatment, however, there was renewed tumor activity, including new lesions as well as regrowth of old lesions. The patient progressed rapidly, despite a series of subsequent therapies, and died.

“The tumor had a remarkable, although incomplete, and rapid, although transient, response to inhibition of the hedgehog

pathway with GDC-0449,” Dr. Rudin and his colleagues noted (N. Engl. J. Med. 2009 [doi:10.1056/NEJMoa0902903]).

“The regression is notable because of the tumor burden and the extent of metastasis in this patient, with substantial soft tissue and bony tissue involvement and clinically significant bone marrow compromise, and underscores the primary role that the hedgehog pathway played in maintaining and driving the growth of this patient’s tumor,” they added.

Examining the possibility of acquired resistance to hedgehog pathway inhibitors will be key in future studies, they

noted. The potential adverse effects of hedgehog pathway blockade in children must also be delineated, as they are the largest population of patients with medulloblastoma.

Dr. Dlugosz reported receiving consulting fees from Merck & Co. and grant support from Pfizer Inc. Dr. Von Hoff reported receiving clinical research funding from Genentech Inc. Dr. Rudin reported receiving research funding and a BioOncology Grant Program Award from Genentech, as well as a clinical scientist award in translational research from Burroughs Wellcome Fund. Dr. Talpaz had no conflicts to report. ■