

BCC Responds to Hedgehog Signal Suppression

BY BETSY BATES

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SAN DIEGO — A custom-designed inhibitor of a mutation in the Hedgehog signaling pathway stimulated antitumor activity in eight of nine patients with locally advanced, multifocal, or metastatic basal cell carcinoma in phase I interim trial results presented at the annual meeting of the American Association for Cancer Research.

Patients in the small, ongoing trial experienced healing of their lesions, diminishment of pain and fatigue, and improvement in dyspnea while taking the study drug GDC-0449 for periods ranging from 120 to 438 days.

"These responses were pretty dramatic, [beginning] within 2-3 weeks of starting the drug," said Dr. Daniel D. Von Hoff, senior investigator and director of translational research for the Translational Genomics Research Institute in Scottsdale, Ariz.

Basal cell carcinoma is the most common malignancy in humans, diagnosed in approximately 1 million U.S. patients per year. While it typically grows slowly and can be managed by local excision or ionizing radiation, it may infiltrate surrounding tissue. In rare cases (less than 0.1%), it becomes metastatic, most commonly to the lung, liver, and/or bone.

The first three patients enrolled in the study received daily doses of 150 mg, 270 mg, and 540 mg, respectively, of GDC-0449, a synthetic, revved-up version of the naturally occurring Hedgehog pathway antagonist cyclopamine. When antitumor activity was confirmed, six more patients were enrolled, all receiving the 150-mg/day dose.

The average patient was aged 61 years (range 42-85 years). Eight were men.

All had undergone surgery (some as many as 20 operations) for their basal cell carcinoma. Four had received radiation, and three were given chemotherapy. Five patients had metastatic disease, two had locally advanced disease of the ear, and two had multifocal disease.

Among four of the patients with metastatic disease, two had a confirmed partial response, one had stable disease, and one progressed while on the study drug and died of his disease. It is too early to assess the response of one recently enrolled patient with metastatic disease, according to Dr. Von Hoff.

In four patients with clinically evaluable locally advanced or multifocal disease, two had a complete response and two had stable disease, meaning that their skin lesions were not advancing.

Metabolic responses to chemotherapy were demonstrated in all five patients who had undergone positron emission tomography evaluations at the time of the presentation, Dr. Von Hoff reported during a late-breaking session.

"Toxicities were relatively mild," he said; they included dysgeusia, an alteration in taste sensations; mild alopecia; mild weight loss; and hyponatremia.

The drug's development represented what Dr. Von Hoff called, "the essence of translational medicine." Molecular biologists first discovered that aberrance in the

Hedgehog signaling pathway triggered when patched (PTCH) or smoothed (SMO) gene mutations caused an acceleration of cell growth that proved instrumental in the development of either sporadic or hereditary basal cell carcinoma.

Nature then played a role, he noted.

Serendipitously, it was discovered that cyclopamine, a naturally occurring inhibitor of the SMO mutation, could be found in pregnant ewes that ate corn lilies in the western United States and subsequently

gave birth to cyclopslike lambs with over-size heads and a single, central eye.

Genentech Inc., in conjunction with the Curis Inc., developed a synthetic version of cyclopamine 100 times more potent than the version found in corn lilies, naming the agent GDC-0449.

Patients, including Subject #1 in the phase I study, "knew the drug was coming and hung on." Although metastatic basal cell carcinoma is very rare, its prognosis is poor, with a mean survival of ap-

proximately 5 months, said Dr. Von Hoff.

Formal discussant Dr. Ervin Epstein of the Children's Hospital Oakland (Calif.) Research Institute noted that many unanswered questions remain about GDC-0449, but he said that, as a "card-carrying dermatologist," he is "full of optimism ... that help is on the way."

Dr. Von Hoff receives research grant support from Genentech, developer of GDC-0449. Dr. Epstein is a consultant for Genentech and owns stock in Curis. ■



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