

# Gleevec May Be Effective for Mucosal Melanomas

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NEW YORK — Is Gleevec a reasonable therapeutic choice for melanoma?

The question has gotten a fair bit of research attention over the last few years, and for a few specific types of melanoma the outlook is cautiously optimistic, Dr. Philip LeBoit said at the American Academy of Dermatology's summer academy 2007 conference.

Gleevec (imatinib mesylate) will probably not become a first-line therapy for cutaneous melanoma, but it may work for mucosal melanomas, acral melanomas, and others that share genetic similarities to the sort of gastrointestinal lesions that have been highly responsive to this landmark drug. A number of case reports point in this direction, said Dr. LeBoit of the departments of pathology and dermatology at the University of California, San Francisco.

Gleevec was the breakthrough agent representing a class of drugs that target protein tyrosine kinase (PTK), an enzyme that plays an essential role in the proliferation and migration of many kinds of cancer cells. Gleevec-responsive tumors tend to have specific genetic profiles, showing mutations of the c-kit and abl genes, among others.

The drug has been particularly effective against GI stromal tumors, which have distinct c-kit mutations. The good news is that as dermatopathologists and molecular biologists explore genetic profiles of various kinds of skin cancers, they are finding that some melanoma types, especially mucosal melanomas, share these c-kit mutations, said Dr. LeBoit, who has no financial relationship with Novartis, the manufacturer of Gleevec.

"Mucosal melanomas have a lot of c-kit mutations. These tumors are almost impossible to resect. They may be candidates for Gleevec or second-generation drugs of that class," he said. Most mucosal melanomas are positive for c-kit mutations, as are roughly one-third of all cutaneous melanomas.

Dermatopathologists at the M.D. Anderson Cancer Center, Houston, studied before- and after-treatment biopsy specimens from 13 patients with malignant melanoma who were given Gleevec at a dose of 400 mg twice daily for 2 weeks. The drug produced a significant decrease in PTK expression in the tumor tissue, as well as a reduction in the number of malignant melanocytes and the intensity of their proliferation (J. Cutan. Pathol. 2006;33:280-5). The investigators noted that one of the 13 patients showed a "durable clinical response."

Brazilian researchers looked at the impact of Gleevec in tissue samples from uveal melanomas, the most common intraocular form of melanoma. Nearly 80% of the 55 tumors examined were positive for c-kit mutations. Gleevec reduced proliferation of the tumor cells in culture (J. Carcinog. 2005;4:19).

A recent phase II trial, however, showed little clinical impact from Gleevec therapy for cutaneous melanomas (Cancer 2006;106:2005-11).

Dr. Lynn Schuchter of the University of Pennsylvania, Philadelphia, is currently studying Gleevec in combination with temozolomide in 63 patients with advanced melanoma, Dr. LeBoit said. So far, the toxicity profile suggests that the PTK inhibitor is a viable adjunct with no significant added side-effect burden. Clinical outcomes data are not yet available.

It may be that Gleevec only works in tumors with very specific genetic profiles, and the key is to identify tumor suscepti-

bility before treatment, in a way analogous to antibiotic susceptibility testing for microbial pathogens. This, said Dr. LeBoit, is the general trend in cancer therapy: the application of tools like immunohistochemistry and comparative genomic hybridization to subclassify tumors based on their genetic features.

"Cancer is fundamentally a disease of the genome. Something has to be wrong with the cells' DNA. Most cancer cells have gains or losses of whole chromo-

somes or major parts of chromosomes," he noted.

A few years ago, dermatopathologists were dependent almost exclusively on microscopy because there simply were no practical molecular diagnostic tools, but that scenario is changing fast. Diagnosis of skin cancers like melanoma "is not a simple positive-or-negative, yes-or-no process. We really need to get into the nuclei of cells to see what is going on," Dr. LeBoit said. ■

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