KIT Mutations Seen in Acral/Mucosal Melanomas

BY KERRI WACHTER
Senior Writer

CHICAGO — KIT gene mutations that are susceptible to imatinib occur in some acral and mucosal melanomas, opening up new therapeutic options for patients with melanoma, according to a study presented as a poster at the annual meeting of the American Society of Clinical Oncology.

KIT mutations were found in 23% of acral melanomas and 16% of mucosal melanomas, reported Dr. Michael C. Heinrich, professor of medicine at the Oregon Health and Science University, Portland, and his colleagues. The mutation frequency was greater among tumors of the anorectum, vulva, and vagina (44%) than among the head and neck (8%).

In contrast, KIT mutations accounted for only 2% of cutaneous melanomas and for 8% of conjunctival melanomas. No mutations were found in an additional 60 choroidal melanomas.

"Based on our study, approximately 40%-50% of all types of melanoma have an oncogenic mutation that could be treated with drugs that are or will be in clinical studies within the next 18 months," Dr. Heinrich said in an interview.

For the study, DNA from archival melanomas was amplified by polymerase-chain reaction (PCR) and the products were screened for mutations in KIT exons 11, 13, 17 (n = 189), BRAF exon 15 (n = 116), and NRAS exons 1 and 2 (n = 117). Mutations were confirmed by direct sequencing.

In addition, immunohistochemistry for CD117 (KIT) was performed on a subset of cases. Lastly, the researchers assessed increases in KIT copy number in specific melanoma subtypes using quantitative real-time PCR.

Six of seven KIT mutations identified were of the type predicted to be sensitive to imatinib (Gleevec). KIT mutations did not overlap with NRAS mutations—which were also common in acral and mucosal tumors—or with BRAF mutations, which were absent in mucosal tumors.

"In the not too distant future, we envision that advanced melanoma tumors would be routinely tested for these types of mutations and the results used to make clinical decisions about the best medical treatment. This would be similar to the existing breast cancer model where ER [estrogen receptor] and HER2 [human epidermal growth factor receptor 2] testing are routine pathology tests that are used to individualize treatment programs," said Dr. Heinrich.

Imatinib is indicated for the treatment of Philadelphia chromosome–positive chronic myeloid leukemia, Philadelphia chromosome–positive acute lymphoblastic leukemia, myelodysplastic/myeloproliferative diseases, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, and KIT-positive gastrointestinal stromal tumors.

Using a PCR-based assay, the researchers found that KIT was increased in acral and mucosal melanoma cases, though most of the tumors with increased KIT did not have a mutation. Extra KIT copies were not as common in cutaneous and conjunctival tumors. KIT (CD-117) expression was detected in 39% of 105 tumors; however, there was no correlation between CD-117 staining and tumor genotype. KIT mutations of the type known to be sensitive to imatinib do not necessarily correlate with either KIT copy number or CD-117 expression, the researchers noted.

The study was prompted by a recent rectal melanoma case in which a patient with a KIT mutation had a dramatic response to imatinib.

Dr. Heinrich reported that he has received research funding from Novartis and Pfizer Inc., is a consultant for Novartis, and has equity interest in MolecularMD. One of his coauthors has received research funding from Novartis and Pfizer and is a consultant for Novartis. ■

N-Acetylcysteine May Block UV-Induced Oxidative Damage to Nevi

BY BRUCE JANCIN
Denver Bureau

KYOTO, JAPAN — Prophylactic oral *N*-acetylcysteine has shown early promise as a novel melanoma chemoprevention strategy, said Dr. Douglas Grossman.

Taking *N*-acetylcysteine (NAC) episodically in anticipation of a day at the beach or before other heavy sun exposure may prevent UV-induced oxidative damage to melanocytic nevi, thereby reducing the long-term risk of malignant transformation, explained Dr. Grossman at an international investigative dermatology meeting.

The drug targets oxidative damage, a specific oncogenic pathway that is induced by UV irradiation. NAC has the ability to sidestep the inherent drawbacks of daily chemopreventive therapy, including compliance problems and drug side effects, said Dr. Grossman of the University of Utah, Salt Lake City. And sunscreens alone seem inadequate for melanoma prevention; in fact, some studies have shown a higher incidence of melanoma in sunscreen users, he said.

NAC is an ideal drug to study for chemoprevention. It has a relatively short serum half-life of 5.5 hours. It is rapidly metabolized to cysteine and converted to glutathione, a potent antioxidant that is depleted by UV.

"NAC is well characterized, cheap, cell-permeable, and has a safety record already demonstrated in humans," the dermatologist noted.

Other investigators have already shown that NAC is useful in preventing oxidative damage in the skin. It is FDA approved for the treatment of toxicity from acute acetaminophen overdose. More recently, it has been used to prevent intravenous contrast-induced nephropathy.

In mouse studies, Dr. Grossman and coworkers have demonstrated that NAC prevents UV-induced formation of the carcinogen 8-oxoguanine and delays onset of UV-induced melanoma (Clin. Cancer Res. 2007;13:5952-8).

In Kyoto, he presented the first clinical study of NAC for melanoma chemoprevention. It involved eight patients who underwent biopsy of a nevus prior to administration of a single 1,200-mg oral dose of NAC. Three hours after NAC administration, a second nevus was removed. The nevi were then irradiated ex vivo with UV at 4,000 J/m^2, which investigators calculated as being roughly equivalent to spending an afternoon outdoors in Utah under a summer sun.

When the nevi were analyzed 24 hours post UV exposure, the control samples showed roughly a 50% reduction in glutathione levels and an increase in 8-oxoguanine, compared with baseline. In contrast, the nevi exposed in vivo to NAC showed no depletion of glutathione and no rise in 8-oxoguanine in three of eight patients.

In hindsight, Dr. Grossman said, the analysis probably should have been done 48 hours post UV exposure rather than at 24 hours. The earlier mouse studies suggested oxidative stress and damage were at their maximum levels at the 48-hour time point.

"We see this as a pilot study in which we had some moderate success in a small number of patients. We're now poised to do a second trial using the 48-hour time point, which we think will be much more robust," Dr. Grossman said at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

Also planned are clinical trials looking at NAC's protective effect in response to UV irradiation in vivo. The possibility that NAC is protective when taken following UV exposure is also worthy of investigation, he added.

The optimal dose of NAC for chemoprevention remains unknown. The 1,200-mg dose used in this study was well tolerated. "Higher doses are probably safe, but we don't know if they'd confer greater protection or not, so we'll probably stick with 1,200 mg," said Dr. Grossman.

His study was funded by the university's Huntsman Cancer Institute. ■

DNA Repair Genes Help Predict Melanoma Survival

BY KERRI WACHTER
Senior Writer

CHICAGO — Single nucleotide polymorphisms in DNA repair genes may help predict not only metastatic capacity but also survival in patients with primary cutaneous melanoma, according to a 400-patient study presented as a poster at the annual meeting of the American Society of Clinical Oncology.

Dr. Dirk Schadendorf of the skin cancer unit of the German Cancer Research Center in Heidelberg, Germany, and his coauthors genotyped 13 single-nucleotide polymorphisms (SNPs) from eight different DNA repair genes in 400 cutaneous melanoma patients. Average patient follow-up was 3.7 years, with 46% of patients having metastasis during that period.

The researchers found that melanoma patients with the AA genotype for the R399Q XRCC1 polymorphism showed better overall survival (hazard ratio, 0.32; P = .03) and metastasis-free survival (HR, 0.40; P = .007) compared with patients who were heterozygous and homozygous (GG). However, survival following metastasis was comparable between the groups.

The study also found that patients with AG and GG genotypes for the –1842 XRCC3 polymorphism (1843bp 5′ of the start codon in the promoter region) showed decreased survival following metastasis, although these differences in mortality after metastasis were significant only for the AG genotype (HR, 1.99; P = .003 [for AG]; HR, 1.53; P = .5 [for GG]) as was mortality overall (HR, 1.68; P = .02 for AG), compared with patients who were homozygous (AA). Metastasis-free survival did not differ between the groups.

No association was found for the other nine SNPs.

"Genetic stability, at least during a specific phase of tumor development, appears to be necessary for a malignant melanoma cell to give rise to metastasis. Accordingly, impaired repair functionality could account for reduced metastatic capacity, better metastasis-free survival, and overall survival as observed in patients homozygous for the variant allele for the R399Q XRCC1 and the K751Q ERCC2 polymorphisms in our study," the researchers wrote.

'Genetic stability, at least during a specific phase of tumor development, appears to be necessary for a malignant melanoma cell to give rise to metastasis.'

"Our data support the concept that overall survival is a sum of factors influencing time from diagnosis of the primary [cancer] to first relapse and factors contributing independently after tumor progression to final outcome," they wrote.

The researchers reported that they had no conflicts of interest. ■