**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 melanomas have an oncogenic mutation that would 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 the incidence of 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 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 disorders, hyperesinophilic syndrome and/or chronic eosinophilic leukemia, dermatomyositis, and gastrointestinal stromal tumors.

Using a PCR-based assay, the researchers found that KIT was increased in acral and mucosal melanoma cases. However, 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., and is a consultant for Novartis.

---

**N-Acetylcysteine May Block UV-Induced Oxidative Damage to Skin**

**By Bruce Jancin**

**Denver Business Journal**

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 skin, 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 5-5.5 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 over-dose. 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 (Clim. Cancer Res. 2007;13:5952-8).

In Kyoto, he presented the first clinical study of NAC for melanoma chemoprevention. It involved eight patients who were givenNAC by a neus prior to administration of a single 1,200-mg oral dose of NAC. Three hours after NAC administration, a second neus was removed.

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.

"I think our group is the only one yet to show that UV-induced skin damage is prevented by NAC," he said. The study also planned an internal trial 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 study also showed that NAC for skin damage prevention 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 increases in KIT copy number, so we’ll probably stick with 1,200 mg," said Dr. Grossman.

His fund was supported 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 colleagues genotyped 13 single-nucleotide polymorphisms (SNPs) from eight different DNA repair genes in 400 cutaneous melanoma patients. Average patients follow-up was 5.7 years, with 46% of patients having metastasis during that period.

The researchers found that melanoma patients with the AA genotype for the R39Q XRC3 polymorphism showed better overall survival (hazard ratio, 0.32; P = .03) and metastasis-free survival (HR, 0.40; P = .007) compared to patients who were heterozygous and homozygous (GG). However, survival following metastasis was comparable between the groups.

The study also showed that patients with AG and GG genotypes for the –1842 XRC3 polymorphism (1843G vs. 1843T 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, 0.39; 95% CI, 0.15 vs. 5; [for GG]) as was mortality overall (HR, 1.68; P = .02 for AG), compared with patients who were homozygous (AA). Meta- static-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."

"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 XRC1 and the K71Q XRC2 polymorphisms in our study," the researchers wrote.

"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.