SESSION 7

S20. Cancer Chemoprevention: Strategies to Save our Skin

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The incidence of skin cancer has been increasing at an alarming rate with an estimated 1.2 million cases in 2001; accounting for 40% of all cancer diagnoses. The majority of skin cancers are nonmelanoma (NMSCs) and include epidermal keratinocyte derived squamous cell (SCC) and basal cell carcinomas (BCC) both of which are closely associated with chronic exposure to ultraviolet light (UV). A pre-malignant lesion or actinic keratosis (AK) has been identified for SCC, but not for BCC. AKs are far more common in the population than SCC with a transformation rate of 6-10% over 10 years providing an excellent target for the development of skin cancer chemoprevention strategies. Although only 4% of skin cancers are melanomas, melanoma is the most deadly form of skin cancer. Dysplastic nevi, a likely precursor of melanoma, are also potential targets for chemoprevention. While vitally important to the reduction of skin cancer mortality, chemoprevention studies of melanoma have been limited.

Cancer chemoprevention can prevent or delay the occurrence of cancer in high-risk populations, such as those with premalignant lesions or previously resected cancer, using dietary or chemical interventions. We have developed chemopreventive strategies that have rational mechanisms of action and demonstrate activity in pre-clinical models of skin cancer. Pre-clinical models include *in vitro* cell culture systems as well as *in vivo* animal models of skin carcinogenesis. Promising agents from pre-clinical models proceed to phase I, II, and III trials in subjects at high-risk of developing skin cancer.

Exposure to UV light induces a number of molecular pathways and results in specific genetic alterations (i.e. mutation of p53) that are likely critical to progression from normal skin to precancer and ultimately to cancer. These UVB-induced changes serve as a basis for the development of chemopreventive agents. Targets include inhibition of polyamine synthesis, inhibition of prostaglandin synthesis, specific retinoid receptors, as well as inhibition of specific components of the Ras and MAP kinase signal transduction pathways. Furthermore, we have shown that epidermal cell proliferation, apoptosis, altered expression of retinoid receptor expression, and mutation of the p53 gene and expression of p53 protein are associated with various stages of UV-induced skin carcinogenesis.

Agents under study include the following; epigallocatechin gallate (EGCG), a green tea catechin with antioxidant and sunscreen activity, as well as UVB signal transduction blocking activity; perillyl alcohol, a monoterpene derived from citrus peel that inhibits Ras farnesyltaion; difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase and polyamine synthesis; novel retinoids that target retinoid X receptors (RXR) and AP-1 activity; and nonsteroidal anti-inflammatory agents that inhibit cyclooxygenase and prostaglandin synthesis.

We have performed a series of Phase I, II, and III clinical trials in high-risk subjects with multiple AK. For example: a phase III randomized trial of oral retinol resulted in a 32% reduction in the risk of developing a subsequent SCC. Similarly, a phase II randomized trial of topical DFMO resulted in a reduction in AK number, suppression of polyamine synthesis, and a reduction in p53 protein expression. Our ultimate goal is to develop chemopreventive agents that can be used in combination and/or be incorporated into sunscreens improving chemoprevention efficacy and a reduction in skin cancer incidence.