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OVERVIEW

Candidate Chemoprevention Agents in Clinical Trials

Epithelial cancers are the major cause of cancer-related deaths. Despite extensive research efforts, the survival rate for these cancers has not improved in the last two decades. Chemoprevention, the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the carcinogenic process from premalignancy to invasive cancer, is a new direction for the control and prevention of this disease.

The rationale for chemoprevention is based on the concepts of field cancerization and multi-step carcinogenesis. "Field cancerization" describes the field-wide damage to tissues exposed to a common carcinogen (*i.e.*, tobacco smoke in the aerodigestive tract), while "multi-step carcinogenesis" refers to the complex molecular and biochemical changes through which premalignant lesions develop into frank malignancy. Studies of the basic mechanism of chemoprevention have focused on efforts to control the early stages of the carcinogenic process. Chemoprevention is based on the ability of chemoprevention agents to control cellular differentiation and proliferation in epithelial tissues.

Data from *in vitro*, animal, and epidemiologic studies strongly support the role of retinoids and carotenoids in preventing epithelial carcinogenesis. Retinoids are well-established agents for control of epithelial cell growth and differentiation *in vivo* and *in vitro*. They can suppress carcinogenesis in a variety of epithelial tissues including the skin, trachea, lung, and oral mucosa. Recent investigations suggest that retinoids modulate or inhibit carcinogenesis by directly modulating gene expression through mediation of nuclear retinoic acid receptors. The mechanism of action for carotenoids and other agents is also unclear but may be related to their antioxidant properties.

Currently, the only definitive endpoint of chemoprevention studies is cancer incidence. This unfortunately leads to large sample sizes and long durations which make these trials so very expensive. Other possible endpoints are a mixed group known as intermediate study endpoints. These endpoints include changes in premalignant lesions, histologic characteristics, and biologic markers, also known as biomarkers. Intermediate endpoints are used primarily in Phase I and Phase II studies to indicate preliminary drug activity. Intermediate endpoint data are often used in the selection process of new drugs for Phase III trials. As yet, however, no intermediate endpoint marker reveals short-term changes significantly correlated with long-term cancer incidence. A potential biomarker relevant to radiation-exposed patients will be discussed.

The study populations for chemoprevention trials most frequently consist of those at high risk from acquired or genetic risk factors, or those at high risk due to previously cured cancers. Second primary cancers frequently develop in patients already cured of an upper aerodigestive tract cancer.

Although chemoprevention is not yet established as a standard approach, the results of reported trials are very promising and have raised tremendous interest in this strategy for cancer prevention. The aim of this session is to provide a comprehensive review of chemoprevention agents which may prove more effective and less toxic, thus furthering the use of this clinically valuable approach to the control of invasive epithelial cancer.

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