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OVERVIEW

Chemoprevention

The term "cancer chemoprevention" refers to the prevention of cancer by intervention with chemicals before malignancy (*i.e.*, invasion). Bladder cancer is a good model system since patients presenting with superficial transitional cell carcinoma (TCC) are at risk of recurrence following treatment. Although recurrent tumors are responsible for high treatment-related morbidity, it is progression that has the greatest potential for mortality and presents the greatest opportunity for intervention by chemopreventive agents. Thus chemopreventive intervention in the bladder as considered here will encompass initiation through progression to higher grade or stage.

The reports included in the session, "Chemoprevention," focused on chemopreventive agents both in chemically induced experimental bladder cancers in animal model systems, and in human trials. Synthetic retinoids have been shown to be effective in rodent bladder models and preliminary data show that *N*-(4-hydroxyphenyl)retinamide (4-HPR) and 13-*cis*-retinoic acid (CRA) may modify the outcomes of patients with resected superficial bladder cancers. Studies describing 2α-difluoromethylornithine (DFMO), an ornithine decarboxylase (ODC) inhibitor, and oltipraz, an electrophilic detoxication enzyme inducer, in animal and human trials were presented as well.

Dr. Richard C. Moon (University of Illinois) presented data on the chemopreventive efficacy of several agents in the OH-BBN-induced urinary bladder cancer model system in mice. Chemopreventive agents were supplied in the diet either alone or in combination. DFMO, piroxicam, oltipraz, and sodium molybdate effectively inhibited the incidence of TCC when supplied as single agents. 4-HPR was ineffective. Two-agent combinations which showed increased efficacy were outlined and compared to three-agent combinations. The three-agent combinations were, in general, no more effective than two-agent combinations, but all combinations significantly reduced bladder cancer incidence even when single agent administration did not.

The results of a pilot study investigating the ability of 4-HPR to affect the outcome of previously resected superficial bladder cancer were discussed by Dr. Andrea Decensi (National Institute for Cancer Research, Genoa, Italy). Using aneuploidy and cytology as intermediate endpoints, patients were treated with 4-HPR and compared with non-randomized, untreated control patients. The proportion of patients with aneuploid stemlines in bladder washed cells decreased for the experimental group and increased in the controls. Suspicious or positive cytology decreased in the 4-HPR-treated group and increased in the control group. Some adverse reactions were noted and discussed; however, preliminary data suggest that 4-HPR may affect the DNA content and abnormal cytology following resection for a previous incidence of superficial bladder cancer.

Dr. George R. Prout, Jr. (Massachusetts General Hospital) discussed the National Bladder Cancer Group's study of CRA in the chemoprevention of superficial bladder cancer. CRA had previously been shown to be effective in suppressing or preventing bladder tumor growth in experimental animal models as well as demonstrating efficacy in human oral leukoplakia and aggressive, recurrent laryngeal papillomatosis. Treatment with CRA was scheduled to last six months and the observed success rate for the first 19 evaluable patients was 16% out of an objective rate of 80%. Due to severe reactions, treatment failures, and the low numbers of patients, the study was terminated before the prescribed time set out in the protocol.

A prospective clinical trial to examine the chemopreventive capacity of DFMO in patients with resected superficial bladder cancer was described by Dr. Charles L. Loprinzi (Mayo Clinic). DFMO, an irreversible ODC inhibitor, has been shown to inhibit carcinogenesis in a variety of animal tumor systems and may be ideally suited to a bladder chemoprevention study as it is excreted unchanged in the urine, allowing it to bathe uroepithelial cells for prolonged periods of time. The biological and clinical properties of superficial TCC render it especially susceptible to the effects of ODC blockade as well as provide a starting point for initial preventative efforts. Oral DFMO has been studied in humans and dosages have been identified which will allow prolonged administration without significant side effects. The rationale for a prospective study of DFMO in patients with completely resected, low-grade, superficial, or superficially invasive tumors was discussed in detail.

Dr. George P. Hemstreet III expanded on the material he presented on intermediate endpoint markers

during an earlier session on detection (see overview by Dr. Melamed). Experimental data on the use of F- and G-actin as intermediate endpoint markers were discussed in detail.

The induction of electrophilic detoxication enzymes, resulting in the reduction of carcinogen–DNA adduct formation and cytotoxicity, appears to be an important component of the anticarcinogenic action of dithiolethiones, including oltipraz. Dr. Thomas Kensler (Johns Hopkins School of Hygiene and Public Health) reviewed the mechanisms of chemoprotection by oltipraz. While mechanistic studies have not been conducted in most model systems, possible mechanisms to explain the observed protective effects of oltipraz were clearly outlined and discussed. Animal models, available bioassays, and mechanistic and pharmacokinetic studies collectively suggest that oltipraz may be an excellent candidate for chemoprotection trials for the suppression of recurrent bladder neoplasms.

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