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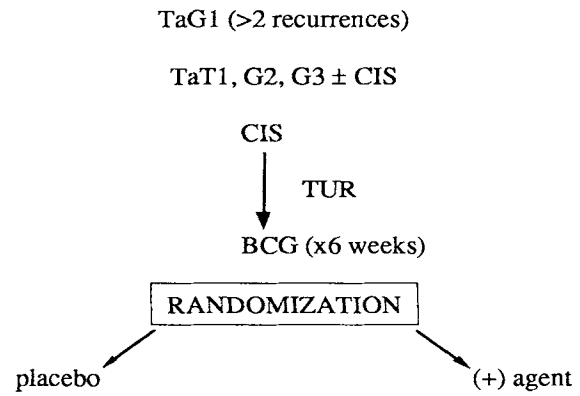
PANEL STATEMENT

Intervention Strategies for Chemoprevention of Bladder Cancer

The panel was charged with developing a framework for bladder cancer chemoprevention trials. Many interesting and provocative discussions focused on identifying: (1) target population(s); (2) study endpoints; (3) chemoprevention agent(s); and (4) biomarker(s) of malignant and/or premalignant disease. Establishing inclusion and exclusion criteria for intervention trials was also addressed.

The focus of chemoprevention trials should be patients with superficial bladder cancer and thus include those with at least two documented recurrences of TaG1 disease, as well as patients with carcinoma *in situ* (CIS) or TaT1, G2, G3 ± CIS. Since chemopreventive agents have little if any cytotoxic activity, eradication of all malignant and premalignant disease by transurethral resection (TUR) and intravesical Bacillus Calmette-Guerin (BCG) therapy would be critical. Although the efficacy of BCG alone has been clearly established and would clearly impact on the treatment arm of an intervention trial, randomization should determine the influence of the agent to be investigated. Given the well known phenomenon of field cancerization in urothelial dyscrasias, neglecting to stabilize the mucosa prior to testing a chemopreventive agent may doom it to failure by implementing it too late along the malignant transformation pathway. Patients would therefore receive intravesical BCG for 6 weeks following TUR, and treatment with the chemopreventive agent(s) would start immediately after the intravesical therapy. Trials will include both treatment and placebo control arms.



Criteria for exclusion include: (1) history of muscle invasive or metastatic bladder cancer; (2) previous intravesical therapy; (3) previous irradiation; (4) transitional cell carcinoma of the prostate; (5) second primary within 5 years; (6) immunodeficiency; and (7) pregnancy.

All-*trans*-4-hydroxyphenyl retinamide (4-HPR) appears to be the agent best suited for clinical intervention trials at this time. There are extensive experimental data in animal models documenting its efficacy in urothelial disease, and a large breast cancer chemoprevention trial in Europe reveals both patient compliance and tolerable toxicity.

Disease recurrence would be the study endpoint. Patients would be followed by standard clinical criteria for superficial bladder cancer including surveillance cystoscopy every 3 months and urine cytology (three voided specimens or one bladder lavage); random biopsies would be optional. Reference laboratories should be used for cytologic interpretation. The length of the trial should be 2–3 years with a 1 year follow-up without treatment to evaluate for possible rebound effect.

A number of biomarkers should be evaluated in the process of an intervention trial including DNA ploidy, DNA image analysis, Le^X, p53, RB, M344, 19A211, EGFR, *ras*, actins and integrins. Only prospective validation will allow promising biomarkers to serve as surrogate endpoints in future chemoprevention trials.

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