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OVERVIEW

Breast Cancer Chemoprevention Clinical Trials

The final session in this meeting included four presentations centered on clinical chemoprevention research and trial design. Drs. Jan Baak and Andrea Decensi presented results of their work on the evaluation and use of potential biomarkers for breast cancer. The use of chemopreventive agents (4-HPR alone or with tamoxifen) in clinical trials in Italy was also described by Dr. Decensi. Dr. Dean Brenner's discussion of the issue of cohort selection for chemoprevention trials was followed by Dr. Andrea Manni's presentation on his research on aromatase inhibitors (aminoglutethimide, fadrazole, and CGS 20267) as potential chemopreventive agents.

Jan P. A. Baak (Free University Hospital, Amsterdam, The Netherlands) described the Multi-Center Morphometric Mammary Carcinoma Project (MMMCP) and efforts to identify and use prognostic factors other than lymph node status and tumor diameter to improve the treatment of women with breast cancer. Dr. Baak detailed several quantitative features associated with proliferation (mitotic activity index, thymidine labelling index, Ki-67, HER-2/*neu*, and % S-phase), differentiation (steroid receptors, mean nuclear area and volume), and cell death (apoptosis rate, % necrosis)—all of which have prognostic value. Many of these factors are being investigated prospectively for their reproducibility and geographic variation, as well as their comparative prognostic value in a trial involving over 3400 women.

Andrea Decensi (National Institute for Cancer Research, Genoa, Italy) presented data from clinical trials with fenretinide (4-HPR) alone and in combination with tamoxifen for the chemoprevention of breast cancer. Trials with 4-HPR have demonstrated that blood levels remain constant for as long as five years, that the drug accumulates in the breast, and that it induces a significant decline in plasma insulin-like growth factor-I levels. Combinations of 4-HPR plus tamoxifen for the chemoprevention of breast cancer are now being studied in randomized trials using a number of circulating growth factors as potential markers.

Dean Brenner (University of Michigan Medical School, Ann Arbor) addressed the issue of selection criteria for breast cancer chemoprevention trial cohorts. Dr. Brenner proposed first using epidemiological risk assessments followed by demonstration of intermediate biomarkers and/or genetic markers as entry criteria for early phase chemoprevention trials. This schema requires that the biomarker be both positive and quantifiable. For breast cancer chemoprevention trials, assessment of epidemiological and/or pathological risk would be followed by screening cellular samples for evidence of early neoplastic changes and prognostic genetic damage.

Andrea Manni (Pennsylvania State University, Hershey) discussed his research on the aromatase inhibitors aminoglutethimide, fadrazole, and CGS 20267. Aminoglutethimide is the most widely tested aromatase inhibitor, suppressing estrogen production to a degree similar to adrenalectomy; however, it can cause moderate toxicity and requires concomitant glucocorticoid administration. Fadrazole suppresses estrogen production to levels similar to aminoglutethimide but at much lower doses and with minimal toxicity and does not require cortisol replacement. It has shown significant antitumor action and is currently on test in Phase III trials. Finally, CGS 20267 has virtually complete selectivity for the aromatase enzyme and suppresses estrogen biosynthesis to a greater extent than other inhibitors.

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