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PANEL STATEMENT

Strategy for Design of Clinical Trials of Chemopreventive Agents

The panel addressed the problems related, on the one hand, to the need to test dozens of chemopreventive agents and agent combinations; and on the other hand, the very high cost and length of time required to test a single chemopreventive agent by presently designed clinical trial methods. It was agreed that the necessary solution to this problem was to set up a new type of clinical trial design. The trials would be short-term (3–6 months treatment, 3–6 months follow-up) and have surrogate endpoint biomarkers (SEB) as their endpoint variable.

These short-term Phase II trials would require a major focus on the SEB, since it was recognized that the quality of the trial would be no better than the quality of the SEB. It was agreed that the SEB should be subjected to QA procedures related to accuracy, precision (reproducibility), sensitivity, and specificity. Controls for tissue biopsy sampling methodology should be defined with attention to variable presence of inflammation and necrosis, and variable cell composition.

It was agreed that the short-term Phase II studies should have both treatment and placebo arms. A placebo arm is only valuable, and should only be used, when effective blinding is possible. These Phase II studies should be blinded as to treatment modality, readout by pathologists, and SEB determination. Blood samples should be taken at all points during the study, and stored as packed RBCs and plasma.

At least two pathologists should perform histological evaluation of biopsies, with a third referee in case of discordance. The pathologists should define the criteria used for the diagnosis of dysplasia and for the evaluation of modulation by a chemopreventive agent. A semi-quantitative evaluation system would be preferred. Some form of simple computerized image analysis system would be desirable.

Patient populations could be from an oral surgical and dental network (3500 oral surgeons are in the US, each with 5–10 leukoplakia patients per year), from VA centers (these could also be a nidus for recruitment across an entire clinical center complex), and from multiple centers across the US.

Study duration would be 6 months, with 6 months follow-up.

Study protocol would include tissue biopsies, scrapings, brushings, needle aspirates, *etc.*, at baseline and at end of treatment at 6 months. A 3 month time point would be desirable. A final 12 month sampling would be necessary.

Study size. This would depend in part on the precision, sensitivity, and specificity of the SEB assay. Ideally, treatment and placebo arms would consist of 50 patients each.

Drugs. Candidate chemopreventive agents include *N*-(4-hydroxyphenyl)retinamide (4-HPR), α-difluoromethylornithine (DFMO), oltipraz, *N*-acetyl-*l*-cysteine (NAC), and combinations of these.

Three aerodigestive sites were covered: oral cavity, lung, and esophagus.

A few specific features of each of these studies were discussed, as follows:

Oral cavity. Only dysplastic oral leukoplakia should be considered.

Bronchus (lung). Image analysis of histological sections lends itself to smears of brushings. Scrapings of lesions and brushings are recommended because sites can be sampled repeatedly. This is not possible with biopsies. Attention should be given to the avoidance of biopsy-induced regression. Better SEB endpoints than metaplasia are urgently needed.

Esophagus. Barrett's esophagus is a well-defined precursor lesion for esophageal adenocarcinoma. It therefore offers a good opportunity for chemoprevention research.

[1] **Stimson P. Schantz, MD—Co-chairman**
[2] **Waun Ki Hong, MD—Co-chairman**
[3] **Charles W. Boone, MD, PhD**
[3] **Gary J. Kelloff, MD**

[1] Memorial Sloan-Kettering Cancer Center
Head and Neck Service
New York, NY 10021

[2] University of Texas
M.D. Anderson Cancer Center
Head, Neck and Thoracic Medical Oncology
Houston, TX 77030

[3] Division of Cancer Prever. ol
Chemoprevention Investigat.
Drug Unit
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892