Intervention Approaches in Early Lung Cancer and Premalignant Disease: Breakout Group Report

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The "intervention" group discussed seven major issues: high risk groups for development of aerodigestive tract cancer; patients versus "participants"; intermediate biomarkers; chemopreventive drug development; high priority compounds; therapy of early lesions; and phase III cooperative group trials.

The group identified several populations at high risk for development of aerodigestive tract cancer: (a) surgically resected stage I non-small cell lung cancer; (b) early stage laryngeal cancer; (c) early stage cancers of other head and neck sites (excluding nasopharynx, paranasal sinuses); (d) small cell lung cancer 2-year cancer-free survivors, based on National Cancer Institute experience indicating a 3-4% rate of developing non-small cell lung cancer per year; (e) chronic smokers with moderate to severe sputum atypia/or dysplasia. It is important to differentiate markers of susceptibility from exposure and to determine risk. Susceptibility markers include appropriate desquame metabolic phenotype and lung cancer families whereas markers of exposure are measures of environmental insults (e.g., tobacco smoke).

The group believed that the high risk populations (a-e) were the best groups for evaluation of markers, intermediate end points, and prevention trials. The issue of patients versus "participants" was discussed emphasizing the difference in "actual" risk and perception of risk. The highest risk groups as indicated above (a-d) are cancer patients who are already in the medical care system with regular scheduled clinic follow-ups. These high risk patients are appropriate for invasive (intensive) biomarker-based clinical trials that would include smaller patient numbers evaluated with serial sputum and bronchoscopic studies. In studies of lower risk "participants," such as smokers or asbestos-exposed subjects, the group recommended that the minimal acceptable samples must include sputum cytology and serum. The latter trials require thousands of subjects and cooperative group approaches for recruitment, data management, and analysis. Issues of perceived risk, which may vary widely, must be dealt with systematically, requiring close collaboration with behavioral scientists.

Intermediate end point biomarkers were discussed at length, reflecting the very early stage of this field. The issue of validation (patterns of marker expression and modulation correlating with invasive cancer development in the context of an intervention trial) was addressed. It was realized that no markers, including sputum atypia and histological dysplasia of the bronchial mucosa, have been validated as an intermediate end point. Validation study designs were outlined including continual adjustments based on the degree of marker correlations. Issues of false positive and false negative patterns were also discussed. Current promising markers include proliferation markers, oncogene products, carbohydrate antigens (e.g., blood group antigens), and genetic markers (i.e., extra copies or deletion of chromosomes). The consensus, however, was that more basic research clearly is required to identify molecular markers of early lesions, especially for adenocarcinoma.

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The group felt strongly that although strict marker validation will take 5-10+ years, it is reasonable and important to use modulation of currently available markers as an end point in phase I or II studies of potential chemopreventive agents. Currently, there are no practical alternatives for selection of promising candidate agents, doses, and schedules for larger phase III trials. Preclinical studies designed to identify potential markers, dose-response studies, and agent combination studies need to continue.

Logistic issues of chemopreventive drug development were discussed. The classic "phase I/II" nomenclature used in therapy trials may not strictly apply to chemoprevention. The definition of maximum tolerated dose should be modified according to risk. Cancer patients at high risk for developing second cancers may tolerate mild to moderate toxicities in contrast to "participants" with a lower risk of cancer who will tolerate less toxicity. Intermediate markers may help with dose selection. The concept of maximum tolerated dose may be inappropriate for biological agents because the dose giving the optimal biological effect may be different than the maximum tolerated dose. Lower dose levels at the optimal biological dose may be more effective than higher doses.

The topic of intraluminal therapy was briefly discussed. The group concluded that further preclinical work was required.

The intervention group recommended that new drug development trials should be small scale, single institution studies with serum and, if possible, tissue pharmacokinetics. Current studies are under way with cis- and trans-retinoic acid with serum and tissue pharmacokinetics in normal and malignant lung tissue in early stage resected specimens.

The intervention group identified the high priority compounds for future study. Retinoids are foremost including low dose 13cRA and the new synthetic analogue fenretinide which clearly has a more favorable therapeutic index in preclinical studies. The Milan Cancer Center has a broad fenretinide program. Their phase I trial has been published and 3 randomized adjuvant trials are ongoing in skin cancer, oral leukoplakia, and a large breast cancer trial. Other clinical work with this agent has been published from the University of Arizona. Two other retinoids are currently in clinical trials. trans-Retinoic
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acid deserves systematic study based on the striking activity in acute promyelocytic leukemia and the apparent increased nuclear receptor affinity. The last promising retinoid discussed was retinyl palmitate based on work from Italy.

Two other agents were discussed. N-Acetylcysteine is a promising early stage inhibitor which has been used extensively for other clinical disorders with minimal toxicity. This agent is under study in the Euroscan 2 x 2 factorial design trial. The isothiocyanate phenethylisothiocyanate is promising based on recent American Health Foundation data in a rodent adenoma model. Further animal toxicity testing with this agent is required, however, before considering clinical work.

Combination regimens were discussed briefly. The retinol/β-carotene regimen was the most promising.

The issues of natural history and treatment of early lesions were discussed, as were problems with the definition of early disease and the gray zone between premalignant and malignant disease (e.g., carcinoma in situ). The intervention group recommended establishing a data registry on early precancerous lesions treated aggressively versus those followed expectantly. Studies in early cancer will inevitably result in increasingly larger numbers of individuals diagnosed with premalignant lesions such as severe dysplasia or carcinoma in situ. No standard treatment exists for these lesions. Protocols should be developed to compare intervention (surgery, photodynamic therapy) with observation. The treatment issues focused on photodynamic and laser therapy for superficial disease.

Logistical and technical aspects of trial designs and conduct were discussed. Invasive marker studies in small high risk populations should continue at the institutional level. Large scale phase III trials require cooperative groups. Input from members of major groups (Southwestern Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, Radiation Therapy Oncology Group) indicated that all groups are now “poised” for a large scale trial in stage I resected non-small all lung cancer. The critical role of participation of thoracic surgeons in these trials was stressed. The need for tissue banks to collect sputum, blood, and other tissue specimens was also reemphasized. The apparent constant risk of second primary tumors would allow a large reservoir of resected patients who have been disease free for years to be enrolled. The intervention group consensus was that low dose 13cRA was the optimal intervention regimen based on Hong’s work in head and neck and due to the shared risk of the upper aerodigestive tract and lung epithelium (field cancerization). The group felt that this study must be expedited due to the potentially narrow window of opportunity for a large scale randomized trial because of emerging results from other lung and head and neck chemoprevention trials.
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