Chemoprevention of Lung cancer

Andrea De Censi, MD
Division of Medical Oncology
Ospedali Galliera, Genova;
Div. Prev, EIO, Milan

Wolfson Institute of Preventive Medicine
Queen Mary University of London
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Giulia Veronesi, MD
EIO; ICH, Milan

Eva Szabo, MD
Division of Cancer Prevention
National Cancer Institute
Current Options for Risk Reduction in High Risk Smokers

- Smoking cessation

- CT screening
  - 20% decrease in lung cancer mortality - National Lung Screening Trial
    - NLST Research Team, NEJM 2011;365:395

Lung Health Study, 14.5 yr f/u
Rationale for Lung Cancer Prevention

• Metastatic cancer is rarely curable
  – US lung cancer 5 yr survival is 16% (5% 1950’s, 13% 1970’s)

• All big killers except for lung are drug-preventable
  – Breast: SERMs, AIs
  – CRC: aspirin, anti COX2, HRT
  – Prostate: 5 alpha RI

• Long preclinical phase with increasing histologic and molecular abnormalities, identifiable populations at risk, window of opportunity for intervention
Efficacy: How Do We Identify Good Agents?

- **Knowledge of mechanism**
  - Example: HPV vaccine and cervical cancer
  - **Need**: understanding molecular pathogenesis

- **Preclinical (in vitro and animal models)**
  - Example: NSAID treated carcinogenesis and transgenic models
  - **Need**: models reflective of complexity of human disease

- **Observational epidemiology (cohort and case-control studies)**
  - Example: ASA and colon cancer incidence/mortality

- **Secondary endpoints from clinical trials (including other diseases)**
  - Example: Tamoxifen and contralateral breast cancer
Prevention may even be harmful!
The beta carotene disaster in smokers

Lung Cancer—Several Diseases Masquerading as One
Implications for Trials Targeting Central vs. Peripheral Carcinogenesis

Normal $\rightarrow$ Hyperplasia/Metaplasia $\rightarrow$ Dysplasia $\rightarrow$ Cancer

Mild/Moderate/Severe/CIS

Squamous
Bronchial dysplasia model

Adenomatous
Helical CT detected nodules

• Molecular pathogenesis different
  - several histologies; molecular differences within histologies (e.g., EGFR vs K-ras)
• Animal models – different responses to same interventions
Targeting Inflammation for Lung Cancer Prevention: Rationale for Corticosteroids

• Animal data showing role for steroids in cancer prevention
  – 1970’s – skin
  – Early 1990’s – lung (oral steroids)
  – Late 1990’s – lung (inhaled steroids)

• Epidemiology/Human data –
  – Mainly negative (but studies of short exposure duration)
  – VA cohort with COPD (n=10,474, 423 lung cancers, 3.4 y followup) – HR 0.39 (95% CI, 0.16-0.96)
    • Parimon T et al., AJRCCM 175:712, 2007
Effect of Budesonide on Mouse Lung Tumorigenesis
Pereira et al., Carcinogenesis 2002

-82% decrease in tumors

-Shift from adenoma to carcinoma
Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia
Lam et al., Clin Cancer Res 2004;10:6502

- Bronchial dysplasia – no effect of 6 mth Rx
- CT-detected lung nodules - 27% vs. 12% resolved (p=0.024)
Peripheral Lung Carcinogenesis Trial Design

202 participants with persistent spiral CT-detected peripheral nodules

Randomize

inhaled budesonide vs. placebo x 1 year

repeat spiral CT

Primary endpoint: shrinkage of lung nodules
Phase IIb Budesonide Chemoprevention Trial
Lesion Specific Analysis

12 months

- Overall response negative, but trend toward regression in non-solid lesions (putative precursors of adenocarcinoma)

5-yr f/u
Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia

- Natural history unknown
- Localized ground glass opacities on CT:
  - AAH 25%; bronchoalveolar ca 50%; invasive adenoca 10%; fibrosis 15% (Nakajima et al., J Comput Assist Tomogr 2002;26:323)
  - AAH 63%; bronchoalveolar ca 34%; scar 3% (Ohtsuka et al., Eur J Cardio-Thor Surg 2006;30:160)
Non-solid nodules – Risk of Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>0-23 Months HR (95% CI)</th>
<th>24-59 Months HR (95% CI)</th>
<th>60-84 Months HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 10+ mm NCN (vs. only 4-9 mm NCNs)</td>
<td>12.8 (9.5-17.2)</td>
<td>4.7 (2.9-7.5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>≥1 NCN w/ Spiculated or Poorly Defined Margins (vs. only NCNs with smooth margins)</td>
<td>4.1 (3.0-5.5)</td>
<td>2.3 (1.5-3.5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>≥1 Persistent NCN (vs. non-persistent NCNs)</td>
<td>N/A</td>
<td>4.8 (2.8-8.3)</td>
<td>N.S.</td>
</tr>
<tr>
<td>≥1 NCN w/ Ground Glass Attenuation (vs. soft tissue attenuation)</td>
<td>0.3 (0.2-0.4)</td>
<td>N.S.</td>
<td>3.1 (1.4-6.6)</td>
</tr>
</tbody>
</table>

**Interpretation:**
Increased long-term risk of ground glass nodules suggests *some* are lung cancer precursors.
Effect of Aspirin on Lung Cancer Mortality
-Rothwell et al., Lancet 2011;377:31

-individual patient data from trials of ASA vs. none

-lung:
f/u 0-10 yrs 0-20 yrs
HR 0.68 0.71
(0.50-0.92, p=0.01) (0.58-0.89, p=0.002)

-adenocarcinoma only

-benefit only after 5 yrs
Evolution of Intraepithelial Neoplasia

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

Adenomatous

If lung cancer death 5+ yrs post ASA use, then stage IV dx at 4+ yrs, Early stage and precursors present at 0-4 yrs post onset ASA use Therefore, ASA effect on precursors should be measurable within one year of use
Phase IIb Aspirin Chemoprevention Trial
Giulia Veronesi, EIO/ICH, Milan

Smokers - >30 pack yr
Age >50
N=128

LD-CT

Persistent non-solid or part-solid nodule(s)

ASA 100 mg qd po x 1 year
Placebo qd po x 1 year

1° Endpoint: #/Size non-solid lung nodules
2° Endpoint: COX/LOX urinary metabolites (PGEM, LTE4), miRNA signature, nodule-based endpoints
myo-Inositol

- Glucose isomer
- Source of several second messengers & signaling molecules
- Dietary sources (grains, beans, fruits, rice)
- Studied in psychiatric conditions (+/-), diabetic neuropathy(+/-), polycystic ovary syndrome (+)
Rationale for myo-Inositol in Lung Cancer Prevention

• **Efficacy**
  - Multiple animal studies show inhibition of carcinogen induced tumors in mice (40-50%)
    - Estensen and Wattenberg, Carcinogenesis 1993;14:1975
    - Hecht et al., Carcinogenesis 2002;23:1455
  - Inhibits carcinogenesis in mainstream/sidestream smoke-exposed A/J mice by 53%
    - Witschi H et al., Carcinogenesis 1999;20:1375
  - **Combination with budesonide ↑↑ efficacy up to 80%**
    - Estensen and Wattenberg, Carcinogenesis 1993;14:1975
    - Witschi et al. Carcinogenesis 1999;20:1375

• **Safety**
  - Used in multiple short term trials for psychiatric and diabetic neuropathy indications – no toxicity reported
  - Generally Regarded as Safe (GRAS) by US FDA terminology
Phase IIb *myo*-Inositol Chemoprevention Trial
Stephen Lam, British Columbia Cancer Agency

Smokers - >30 pack yr
Age 45-79
N=110

Sites:
BCCA, Mayo, NM VA

1° Endpoint: Bronchial dysplasia
2° Endpoint: Multiple biomarkers (gene expression), CT-detected lung nodules

Bronchoscopic Dysplasia

- *myo*-Inositol 9g bid x 6 mths
- Placebo bid x 6 mths
The Future

• **Innovative agents**
  – Understanding molecular mechanisms of lung carcinogenesis (sq and adeno), TCGA of premalignancy
    • Molecularly targeted agents
  – repurposing “old” drugs (eg, ASA, budesonide, metformin)
    • Emphasis on effects in multiple cancers and/or chronic disease states

• **Innovative early phase trial designs**
  – High throughput technologies (e.g., gene expression analysis) to detect drug effects on pathways in a short time frame
Thank you!