Lung Cancer in Women: A Different Disease?

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Case Presentation

• 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier…
Chest X-ray July 2004
Case Presentation

• 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier …

• CT Scan obtained…
CT Scan magnified view

Right Posterior Chest
Case Presentation

• 71 yo woman presented in November, 2005, with abnormal chest X-ray, changed from that of a year earlier …
• CT Scan obtained…
• Referred to Dr. Dalesandro: poor surgical candidate but after period of intensive pulmonary rehab underwent surgery
• 3 cm squamous cell carcinoma with invasion into chest wall
• En bloc pulmonary and chest wall resection
• Pathology….
Case Presentation, continued

- Recovered from surgery
- Referred for adjuvant chemotherapy for T3N0 (Stage IIB) lung cancer
- Received four cycles of taxol and carboplatin – moderately well tolerated
The ALPI trial – overall survival by stage

HR approaches significance

Difference for Stage II substantial
Overall Survival (Panel A) and Disease-free Survival (Panel B)

Highly significant difference for sample size
Back to Our Case…

• April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence…
CT Chest done 3/28/07

Two pleural-based masses
Back to Our Case…

• April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence…
• PET confirmatory with SUV 14
• CT-guided biopsy…
Back to Our Case…

- April, 2007: surveillance CT scan showed 2 new RUL nodes suspicious for local recurrence…
- PET confirmatory with SUV 14
- CT-guided biopsy… + for recurrence
- Referred for radiation therapy; just being completed
Case Presentation, concluding

• In light of local recurrence outlook is guarded
• Awaiting future developments before initiating additional treatments
Lung Cancer Incidence: The Changing Face of a Common Disease

Data Viewed from Perspective of all Cancers

Reported US deaths from the most common cancers in males and females: all ages, 1997

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>91,278</td>
<td>Lung and bronchus</td>
</tr>
<tr>
<td>Prostate</td>
<td>32,891</td>
<td>Breast</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>28,075</td>
<td>Colon and rectum</td>
</tr>
<tr>
<td>Pancreas</td>
<td>13,470</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>12,286</td>
<td>Ovary</td>
</tr>
<tr>
<td>Other sites</td>
<td>103,110</td>
<td>Other sites</td>
</tr>
<tr>
<td>All sites</td>
<td>281,110</td>
<td>All sites</td>
</tr>
</tbody>
</table>
Is Lung Cancer in Women Different?

• Hormone Replacement Therapy may provide a key to the answer....
Ganti study*

• Data on 500 female lung cancer patients
• In women on HRT for at least 6 weeks prior to diagnosis:
  – Lower median age at diagnosis: 63 v. 68 yr
  – Much shorter survival: 39 vs. 79 months
• Hazard ratio for HRT and dying of lung cancer: 1.97….

Survival curves for women with lung cancer based on use of hormone replacement therapy

Ganti study, continued

- Data on 500 female lung cancer patients
- In women on HRT for at least 6 weeks prior to diagnosis:
  - Lower median age at diagnosis: 63 v. 68 yr
  - Much shorter survival: 39 vs. 79 months
- Hazard ratio for HRT and dying of lung cancer: 1.97….
- Differences seen only in women who smoked (86% of population)
- What is the basis for this striking finding??
The Estrogen Receptor Effect

- Lung tumors have estrogen receptors
- Estrogens promote growth of lung tumors in the laboratory
- Estrogen can activate the Epidermal Growth Factor Receptor in lung cancers
- Progesterone may have protective effect
  - Can induce apoptosis (programmed cell death) in lung tumors
Further Analysis: The K-ras effect in Stage I Lung Cancer

• When mutated, encodes for a protein that is carcinogenic
• Mutation at “Codon 12” specific for adenocarcinomas, especially of lung
• Novel protein produced by point mutation activates tyrosine kinase – critical for cell growth – and other pathways as well
• Cigarette smoking probably induces the mutation
K-ras mutations in women with lung cancer

- Studied as part of larger study of K-ras conducted at Mass General*
- Confirmed deleterious effect of K-ras on prognosis
- Startling result: female gender conferred odds ratio of 3.3 of having K-ras mutation in patients with adenocarcinoma of the lung
- Effect of gene mutation…

Effect of Mutation in K-ras on outcome in patients with Stage I lung cancer who underwent curative resection

Huge difference in outcome based on mutation

K-ras in women, continued

- Estrogen can have effect:
  - Adenocarcinoma cells with the K-ras mutation contain estrogen receptors and may be influenced by an estrogen-rich milieu
  - As in the earlier data on women on HRT who get lung cancer
Schematic of Process

Normal lung epithelium → SMOKING → Mutation at Codon-12 in single cell (K-ras) → Neoplastic epithelium

Influence of estrogen

Neoplastic epithelium → Influence of estrogen
Another side to the story: overall survival

- Some data suggest that overall women have better survival stage for stage than men
- ECOG study 1594 tried to identify a superior chemotherapy regimen for Stage IIIB (malignant effusion) and IV (blood-borne metastases) non-small-cell lung cancer
- Four regimens tried; none proved superior
- Subset analysis undertaken to see if women overall did better than men
### Overall Survival

**Table 2. Patient Outcomes for ECOG 1594**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1157 (eligible)</td>
<td>431 (37%)</td>
<td>726 (63%)</td>
<td></td>
</tr>
<tr>
<td>Censored</td>
<td>9 (2.1%)</td>
<td>9 (1.2%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>19</td>
<td>19</td>
<td>0.99</td>
</tr>
<tr>
<td>Median progression-free</td>
<td>3.8 (3.6–4.3)</td>
<td>3.5 (3.0–3.8)</td>
<td>0.022</td>
</tr>
<tr>
<td>survival (mo) 95% CI</td>
<td>3.6–4.3</td>
<td>3.0–3.8</td>
<td></td>
</tr>
<tr>
<td>Median survival time (mo)</td>
<td>9.2 (8.1–10.4)</td>
<td>7.3 (6.8–8.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.1–10.4</td>
<td>6.8–8.0</td>
<td></td>
</tr>
<tr>
<td>Alive at 1 yr (%)</td>
<td>38</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Alive at 2/3 yr (%)</td>
<td>14/7</td>
<td>11/5</td>
<td></td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.

*Wakelee et al. J. Thoracic Oncol. 1 (5): 441-6, 2006*
Analysis of E1594 by Gender*

Survival by Chemo Regimen, Analyzed by Gender

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MST (mo) Women</th>
<th>MST (mo) Men</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: cisplatin/paclitaxel</td>
<td>9.2 (7.0–11.4)</td>
<td>7.6 (6.5–8.7)</td>
<td>0.089</td>
</tr>
<tr>
<td>B: cisplatin/gemcitabine</td>
<td>9.4 (7.8–12.2)</td>
<td>7.4 (6.3–8.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>C: cisplatin/docetaxel</td>
<td>9.2 (7.0–11.3)</td>
<td>6.7 (6.0–8.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>D: carboplatin/paclitaxel</td>
<td>9.0 (7.0–11.6)</td>
<td>7.7 (6.2–9.4)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Values are median (95% confidence interval). ECOG, Eastern Cooperative Oncology Group; MST, median survival time.*

Authors at recent ASCO meeting tried to make a big deal out of these differences.
Is there a conflict?

- Abundance of data of impact of gender and hormones on survival in early stage lung cancer
- Salutary effect of female gender on survival of late-stage disease modest
- ??Different mechanisms of action applicable to the two circumstances: early vs. late stage disease
- Stay tuned…. 
Conclusions

• Lung cancer in women is different biologically
  – Higher expression of K-ras oncogene
  – Effect of endogenous and exogenous estrogens upon K-ras pathway and hormone receptors on tumor cells
  – Women with advanced cancer may do slightly better for unclear reasons
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