Clinical Updates and Issues: Advanced Non-Small Cell Lung Cancer

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formerly of The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

Faculty Biography

Tracy Ruegg, MSN, ARNP, AOCN is Supervising Research Nurse Practitioner at Miami Cancer Institute, Baptist Health South Florida. Just prior to joining the Baptist Health System, she was an adjunct faculty member and preceptor at The Ohio State University College of Nursing and a nurse practitioner in thoracic medical oncology at the James Cancer Hospital and Solove Research Institute where she worked for 18 years.

Ms. Ruegg received her nursing degree at Worcester State College and her advanced nursing degrees from The Ohio State University. Ms. Ruegg is currently a doctoral student specializing in oncologic nursing at The University of Utah.

Ms. Ruegg pioneered the nurse practitioner role within the family and medical oncology practice settings. She was the first advanced practice nurse to perform cancer-related procedures such as bone marrow biopsies, paracentesis, and omaya chemotherapy administration.

Ms. Ruegg has lectured on various topics in nursing and oncology. She served on the NCI Drug Development Task Force and maintains memberships in several national associations. She is published in various nursing publications and has been the recipient of many awards throughout her career.
Lung Cancer Statistics, 2016

- Greatest cause of cancer deaths worldwide
  - 230,390 new cases per year, 15% of US cancer cases
  - 158,890 deaths per year, 27% of US cancer deaths

- More deaths than colon, breast, and prostate cancer deaths combined

(ACS Cancer Facts & Figures, 2016)

Estimated Cancer Deaths by Site

- Lung & Bronchus
- Breast
- Colorectal
- Prostate

ACS Cancer Facts & Figures 2016
Clinical Symptoms and Presentation of Lung Cancer

- Cough
- Dyspnea / wheezing / SVC syndrome
- Hemoptysis
- Pneumonia / unresolved infection
- Pleural effusion
- Hoarseness
- Weight loss
- Night sweats
- Pain
Lung Cancer Screening: NLST

- Clinical symptoms of lung cancer are a late finding
- Advanced tumor stage @ time of diagnosis= palliative treatment
- Low dose CT scan vs. CXR
- Annual screening x 3
- 27% CT vs. 6.2 % CXR (year 1) AND 16.8% CT vs. 5.0% CXR (year 2)
- Decreased advanced stage with increased early stage Dx.

Abele et al, 2011

Diagnostic Techniques

- Adequate biopsy sample
  - Fine Needle Aspiration (FNA) – CORE Bx
  - Bronchoscopy / EBUS
  - Video Assisted Thoracoscopic Surgery (VATS)
  - Mediastinoscopy

- THE ISSUE IS TISSUE!
Lung Cancer Pathology

- Small Cell - 15%
- Non-Small Cell - 85%
  - Adenocarcinoma
    - most common
    - least associated with tobacco
    - Molecular Mutations
  - Squamous cell carcinoma
  - Bronchoalveolar carcinoma / papillary?
  - Large-cell carcinoma
- Mixed tumors
- Carcinoid and rare tumors

Staging of Non Small Cell Lung Cancer

7th IASLC Staging System

<table>
<thead>
<tr>
<th>T and M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>UICC6 and descriptor</td>
<td>N0</td>
<td>N1</td>
<td>N2</td>
<td>N3</td>
</tr>
<tr>
<td>T1 (≤2 cm)</td>
<td>T1a</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T1 (&gt;2-3 cm)</td>
<td>T1b</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T2 (≤3 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T2 (&gt;3-7 cm)</td>
<td>T2b</td>
<td>IA</td>
<td>IB</td>
<td>IA</td>
</tr>
<tr>
<td>T2 (&gt;7 cm)</td>
<td>T3</td>
<td>IB</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T4</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T4 (same lobe involvement)</td>
<td>T4</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (pleural effusion)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Goldstraw et al, 2007
Pulmonary Molecular Testing: 
Next Generation Sanger Sequencing

- FISH analysis: ALK / ROS1 / MET / RET
- EGFR (exons 19-21)
- T790m (exon 20)
- AKT1
- BRAF
- ERBB2, ERBB4
- HRAS, KRAS, NRAS
- HER2

- MEK
- PIK3CA, PTEN
- STK11
- TP53
- FDGF1, FGFR2
- CTNNB1
- DDR2
- MAP2K1
- NOTCH1
- SMAD4

Alamgeer et al, 2013
## Mutational Pathway Patient Characteristics

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Prevalence (%)</th>
<th>More commonly associated patient characteristics</th>
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</thead>
<tbody>
<tr>
<td>RAS</td>
<td>30</td>
<td>Former/current smokers</td>
</tr>
<tr>
<td>EGFR</td>
<td>10–18</td>
<td>Caucasian; 40–55 Asian; East Asian, female, never smokers</td>
</tr>
<tr>
<td>ALK</td>
<td>3–7</td>
<td>Young, never smokers</td>
</tr>
<tr>
<td>ROS</td>
<td>3–2</td>
<td>Young, never smokers</td>
</tr>
<tr>
<td>RET</td>
<td>3–2</td>
<td>Never smokers</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>2</td>
<td>Concurrent with other oncopgenic drivers</td>
</tr>
<tr>
<td>BRAF</td>
<td>3–5</td>
<td>Former/current smokers</td>
</tr>
<tr>
<td>HER2</td>
<td>1–4</td>
<td>Female, never smokers</td>
</tr>
<tr>
<td>RIT</td>
<td>2</td>
<td>Not available</td>
</tr>
<tr>
<td>NTRK1</td>
<td>5</td>
<td>Female, never smokers</td>
</tr>
<tr>
<td>MET</td>
<td>11</td>
<td>Mutually exclusive with EGFR mutations</td>
</tr>
<tr>
<td>FGFR1</td>
<td>1–3</td>
<td>Male, smokers</td>
</tr>
</tbody>
</table>

* Frequencies detected from pts. with unknown mutations; prevalence is an overestimation.

Gower, Wang & Giaccone, 2014

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## Metastatic Disease

- **Stage IV**
- **Metastatic sites:**
  - bone
  - brain
  - liver
  - adrenal glands

**5 year survival**

<1%
Treatment Considerations

- Diagnosis
  - Adequate biopsy sample
- Stage
  - Stage determines treatment
- Treatment
  - In NSCLC, surgery is the cornerstone of treatment
- Prognostic / Treatment factors
  - Performance status (ECOG 0-4)
  - Weight loss (<5-10%)
  - Age/comorbidity
    - Pulmonary
    - Cardiac

First-line Treatment for Metastatic NSCLC

- Palliative Platinum-based chemotherapy
- Adenocarcinoma – Cisplatin/Pemetrexed for PS 0-1; other options are available
- Squamous Cell – Carboplatin/Paclitaxel or Carboplatin/Gemcitabine for PS 0-2; other options are available
- Large Cell – Carboplatin/Paclitaxel/Bevacizumab or Carboplatin/Pemetrexed
- “Maintenance” pemetrexed chemotherapy for non-squamous (Paz-Ares et al. 2013)
  - Progression free survival = 4.3mos v. 2.6 mos
**Molecular Targeted Therapy**

- **Sensitizing EGFR** (epidermal growth factor receptor) mutation
  - **1st Generation**
    - Erlotinib
    - Gefitinib
  - **2nd Generation**
    - Afatinib

- T790M mutant EGFR

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**EGFR TKI Therapy Side Effects**

**Most Common**
- Diarrhea
- Rash,
- Dry skin
- Dyspnea
- Cough
- Nail toxicity
- Paronychia

**Less Common**
- Nausea
- Decreased Appetite
- Stomatitis
- Elevated LFTs
- Hypokalemia

*See erlotinib, gefitinib, afatinib package inserts*
**EGFR TKI Therapy Side Effects**

**Serious Side Effects**

- Interstitial Lung Disease/ Pneumonitis
- QTc interval prolongation
- Cardiomyopathy
- Embryo-fetal toxicity
- VTE

*See erlotinib, gefitinib, afatinib package inserts

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**T790 Mutation Drugs**

- T790 mutation is found on exon 20
- Indicates resistance to EGFR TK Inhibitors
- Median time to resistance of EFGGR ~ 14 mos.
- New Drugs
  - Osimertinib
  - Rociletinib
  (not yet FDA approved)
T790m Therapy Side Effects

- [Same as other EGFR TKI]
  - Diarrhea
  - Rash
  - Dry Skin
  - Stomach upset: Nausea
  - Constipation
  - Decreased Appetite

- Cardiac Toxicities
- Hyperglycemia (with rociletinib)

*see osimertinib package insert*

Molecular Targeted Therapy

**ALK** (anaplastic lymphoma kinase) mutation

- **1st Generation**
  - Crizotinib

- **2nd Generation**
  - Ceritinib
  - Alectinib
ALK Therapy Side Effects

• Most Common
  – Vision Disorders
  – Diarrhea
  – Fatigue
  – N/V, Constipation, Abdominal pain
  – Edema
  – Myalgia
  – Elevated LFTs
  – Cough
  – Rash
  – Headache

*See crizotinib, ceritinib, alectinib package inserts*

ALK Therapy Side Effects (cont.)

Serious Side Effects

• Interstitial Lung Disease/ Pneumonitis
• Hepatotoxicity
• Bradycardia
• Severe Myalgia
• Embryo-fetal toxicity

*See crizotinib, ceritinib, alectinib package inserts*
Molecular Targeted Therapy
Investigational Studies

- **ROS1** – crizotinib approved 03/11/16
- **cMET/ RET** – testing crizotinib
- **KRAS** – no targeted therapy available
- **BRAF** – compassionate use BRAF inhibitors?

Immunotherapy

**Role of PD-1/PD-L1 pathway in suppressing anti-tumor immunity**

Anti PD-L1 Drugs

• Indicated after the use of platinum-based chemotherapy

  – Pembrolizumab
    • (PDL1 positivity required)
  – Nivolumab

*caution use with autoimmune disorders*

Anti PD-L1 Drug Side Effects

Most Common

• Malaise / Fatigue
• Low grade fever
• M/S pain
• Decreased appetite
• Cough
• Constipation
• Enlarged lymph nodes
• Elevated LFTs

*See pembrolizumab and nivolumab package inserts*
Anti PD-L1 Drug Side Effects (cont.)

**Serious Side Effects**

- Pneumonitis
- Immune-mediated
  - Colitis
  - Hepatitis
  - Nephritis
  - Renal Dysfunction / Adrenal Insufficiency
  - Rash
  - Encephalitis
- Embryofetal toxicity
- Serious: Interstitial lung disease; colitis; “…itis”

*See pembrolizumab and nivolumab package inserts*

Current Investigations with Immunotherapies

- Small Cell Lung Cancer
- 1st line therapy for lung cancer
- Combination with chemotherapy
- Combination with 2 different immunotherapy blockades
  - (e.g. PDL1 + CTLA4)
Monoclonal Antibodies

- VEGF (vascular endothelial growth factor)
  - Bevacizumab
    - Only FDA approved with Carboplatin / Paclitaxel chemotherapy for 1st line treatment of Adenocarcinoma
      - Difference in overall survival
- Necitumumab – 1st line therapy with Cisplatin / Gemcitabine for Metastatic Squamous Cell (only)
- Ramucirumab – [VEGFR-2] FDA approved with Docetaxel 2nd line therapy
- Ipilimumab – under investigation

Palliative Care

- Palliative care means more than Hospice
  
  Meticulous attention to:
  - Symptom control
  - Pulmonary symptoms
  - Pain
  - Social support
  - Family/Caregiver needs
Palliative Care and Survival

- **Temel et al (2010)** *Early palliative care for patients with metastatic non-small-cell lung cancer*
  - Increased QoL
  - Decreased depression
  - Decreased EOL hosp. admissions
  - INCREASED SURVIVAL (11.6 mos. vs. 8.9 mos.)

- **Greer et al (2012)** *Effect of early palliative care on chemotherapy use and EOL care in pts. with metastatic NSCLC*
  - No difference between groups in # of chemo cycles
  - Optimized timing of final chemo cycle and smoother transition to hospice = good death

- **Nipp et al (2016)** *Age & Gender moderate the impact of early palliative care in metastatic NSCLC*
  - Males & younger pts. <65 years had increased QoL and Mood

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NCCN Guidelines

- **Guidelines to Wellness**
  - Anxiety/Depression
  - Cognitive Function
  - Fatigue
  - Sleep Disorders
  - Chronic pain
  - Sexual Dysfunction

- Surveillance recommendations to guide f/u care
THANK YOU TEAM

• It takes a Village…

• Nurses: RN/CNP/CNS
• Medical Oncologists
• Radiation Oncologists
• Thoracic Surgeons
• Radiologists
• Pathologists
• Molecular biologists
• Pharmacists
• Social Workers
• Hospice staff

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