Learning Objectives
- To recognize the importance of lung cancer in public health
- To understand how to decrease risk for developing lung cancer
- To understand the difference in the characteristics and treatment of non-small cell (NSCLC) and small cell lung cancer (SCLC)
  - Recognize when treatment is palliative vs. curative

Learning Objectives
- To be able to choose appropriate therapy based on stage of disease and prognostic factors
- To recognize & manage adverse effects to medications used to treat lung cancer
- Don’t need to memorize the tumor staging (e.g., T1 being < 1 cm), number of participants in trials, percent survival

Lung Cancer Incidence
- Types of lung cancer
  - Non-small cell lung cancer (NSCLC): 70-75%
  - Small cell lung cancer (SCLC): 20-25%
- Overall survival for lung cancer has slightly improved over the past 20-years
- ~50% of newly diagnosed lung cancer patients are >70-years old and 16% are >80-years old

Minimizing Risk of Lung Cancer

- Primary prevention
  - Minimize risk factors
  - CARET (carotene & retinol efficacy trial)
  - ATBC (α-tocopherol & beta-carotene)
- Screening

Risk Factors: Smoking

- Greatest cause of cancer in the world
  - Causally related to at least 16 types of cancer
  - 1/3 of all cancer-related deaths annually, with 80% of that mortality related to lung cancer
  - Most smokers do NOT develop lung cancer
  - Smoking causes 85-90% of lung cancer deaths
  - Smoking cessation
    - **greatest intervention to lower cancer rates**
    - risk for smoking-related cancers begins to decrease within 5 years of abstinence
    - risk never reaches that of a non-smoker

Risk Factors

- Other unidentified risk factors are involved
  - Only 1 in 5 smokers get lung cancer
  - 2-9% of men and women, respectively, with lung cancer never smoked

Risk Factors

- Environmental exposure
  - Second-hand smoke
  - Asbestos, radon (underground miners, home?), industrial pollution
  - Genetic
    - 1.3 - 4 fold ↑ risk of lung cancer in nonsmokers whom have a family history of lung cancer
    - Genetic polymorphisms (e.g., CYP)
  - Dietary factors
    - Low intake or low anti-oxidants serum concentrations associated with ↑ risk of lung cancer
    - Led to 4 randomized controlled trials (RCT) to assess antioxidants in preventing cancer, cardiovascular disease or both

Cancer Prevention Strategies

- Primary
  - Prevents a disease from developing in a clinically asymptomatic person
- Secondary
  - Measures that identify and treat asymptomatic persons with preclinical disease
  - Successful if earlier treatment has better outcome & have effective screening methods

CARET (Beta carotene and Retinol Efficacy Trial)

- 18,314 men and women 46 - 74 yo with history of cigarette smoking or occupational asbestos exposure
- Combination of β-carotene 30 mg/day and retinol (retinyl palmitate) 25,000 IU/day evaluated
- ↑ risk of lung cancer among current and former smokers
- ↑ risk of death from lung cancer & CV disease
- Trial stopped early
Carotenoids

- ATBC (Alpha-tocopherol, beta-carotene)
  - 29,133 50 – 69 yo men whom were smokers
  - RCT of placebo, β-carotene 20 mg/day, α-tocopherol 50 IU/day or both for 5-8 years
  - β-carotene arm had ↑ incidence and mortality from lung cancer initially, with no excess risk 4 – 6 years after discontinuing β-carotene
  - α-tocopherol arm ↑ incidence years after treatment
- US Physician’s Health Study
  - 22,071 40-84 yo men 11% current, 39% former smokers
  - Placebo, β-carotene 50 mg QOD, aspirin 325 mg/day or in combination for 12 years
  - no effect on overall incidence of cancer
  - Nutrition Intervention Trial I (China) ↓ stomach and overall cancer mortality w/vitamin E, β-carotene & selenium
  - Has not prevented cancer in > 70,000 subjects

JAMA 2003; 290: 476; Lippman JNCI 1998

Lung Cancer Screening

- Screening with chest x-ray with sputum cytology did not ↓ lung cancer mortality in current or former smokers
  - US Preventive Task Force (USPTF): Benefit not established in any group, including asymptomatic high-risk populations (e.g., older smokers)
  - For detecting lung cancer, sensitivity of low dose computerized tomography (CT) is 4 times greater than chest X-ray. However, CT ↑ false positives, ↑ radiation exposure, ↑ cost
  - Mortality (1-11%) & morbidity (9-44%) from invasive diagnostic procedures in symptomatic patients
  - Role of helical CT being evaluated in NCI-sponsored trial


Signs & symptoms

- Disease-specific: hemoptysis, cough, chest pain, dyspnea
- Non-specific: weakness, malaise, decline performance status

Comparison of Lung Cancers

<table>
<thead>
<tr>
<th></th>
<th>SCLC (20%)</th>
<th>NSCLC (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast growing, aggressive, metastasizes early</td>
<td>surgery has no established role</td>
<td></td>
</tr>
<tr>
<td>responsive to chemotherapy and radiation</td>
<td>&gt;80% respond to chemo</td>
<td></td>
</tr>
<tr>
<td>&gt;100% increase in survival</td>
<td>~10% “cure”</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy indicated in all patients</td>
<td>Grows more slowly</td>
<td></td>
</tr>
<tr>
<td>surgery possible in ~35% of cases</td>
<td>Less responsive to chemotherapy</td>
<td></td>
</tr>
<tr>
<td>30-40% response rate</td>
<td>~25% increase in survival</td>
<td></td>
</tr>
<tr>
<td>very rarely “cured”</td>
<td>Chemotherapy indicated in all patients</td>
<td></td>
</tr>
</tbody>
</table>

5-year Survival with Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td></td>
<td>50-70%</td>
</tr>
<tr>
<td>I</td>
<td>&gt;60-70%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>&gt;40-60%</td>
<td></td>
</tr>
<tr>
<td>IIIA (resectable)</td>
<td>15-30%</td>
<td></td>
</tr>
<tr>
<td>IIIA/B (unresectable)</td>
<td>10-20%</td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>IV (2-yr)</td>
<td>10-15%</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12-15%</td>
<td>6-7%</td>
</tr>
</tbody>
</table>

Histologic Types of NSCLC

- Adenocarcinoma (45-55%)
  - incidence is rising
  - most are peripheral in origin
- Squamous cell (30-40%)
  - most are central in origin
- Large Cell Carcinoma (~15%)
  - diagnosis difficult
  - many diagnosed as poorly differentiated carcinoma
NSCLC: Treatment Planning

- Patient factors
  - Performance status
  - Concomitant illness
  - Stage of disease (TNM staging)

Early stage NSCLC

- Stage I-IIIa, Curative intent
- Surgery
  - Option for those - regardless of age - with adequate cardiac & lung function to tolerate resection
  - 5-yr survival 45-70% (depending on tumor size)
- But many patients die from distant recurrence, suggesting a benefit for systemic chemotherapy

Early stage NSCLC: Chemotherapy

- Meta-analysis in mid 1990s
- No benefit from overall chemotherapy however trials were underpowered & not with good chemotherapy
- Trend toward improved survival with cisplatin led to additional trials
- In 2003-2004, results available from 3 separate randomized controlled trials of 4-cycles of adjuvant chemotherapy vs. observations
  - In Ia-Ila patients mainly, few Ia patients

Br Med J 1995; 311: 899
Early stage NSCLC: Chemotherapy

- All three trials showed an improvement in 5-yr disease-free and overall survival
- 4.1-15% improvement in 5-yr survival...save at least 7000 patients/yr
- Survival benefit with adjuvant chemotherapy in NSCLC BETTER than that with breast cancer
- Fatal toxicity low (0.8%), but only ~50% of patients can finish 4 cycles of chemotherapy
  - led to interest in neoadjuvant (also called induction) chemotherapy


Early stage NSCLC: Adjuvant Chemotherapy

- Cisplatin-based with etoposide, vinorelbine, vinblastine
  - NCCN
  - Cisplatin-vinorelbine (largest survival benefit)
- Carboplatin AUC=6 mg*ml/min; paclitaxel 200 mg/m²


N2 NSCLC

- Involvement of ipsilateral mediastinal or subcarinal nodes
  - poor survival if untreated (e.g., IIIaN2 1-yr survival ~10%)
- Most IIIa patients have N2 disease
- Very heterogenous disease
  - surgery alone has low (4%) 5-yr survival as minority of patients can be completely resected
  - Induction chemoradiotherapy is feasible but postoperative mortality ranges from 3-16%
- With cisplatin/etoposide induction (2 cycles) followed by XRT OR surgery followed by adjuvant chemotherapy (cann...overall survival no different although disease free survival better with surgery
  - Benefit of induction chemotherapy (cisplatin/docetaxel) +/- concurrent XRT with adjuvant chemotherapy (docetaxel X 3 cycles) currently being evaluated

NSCLC: Stage IIIB

- Any T4 or any N3, M0
  - If pleural effusions, frequently treated as stage IV
- Survival
  - Surgery debatable
  - Radiotherapy (5-7% at 5-yr) < induction chemotherapy followed by radiotherapy < concurrent chemoradiotherapy

Advanced NSCLC

- Stage IIIB (pleural effusions) or Stage IV (M1)
  - Common sites: liver, bones, adrenal, brain
  - No treatment: median survival 3.6 months, 1-year survival of 10 - 15%
  - Standard of care for appropriate patients is doublet therapy of platinum with a third-generation chemotherapeutic
    - ↑ in median survival by 6 - 8 weeks and ↑ in 1-year overall by 10%
    - relieves symptoms
    - cost-effective

Chemotherapy for Advanced NSCLC: Patient Selection

- Prognostic factors
  - Performance status
  - 0 or 1: chemotherapy is appropriate
  - 2 - 7: toxicity relative to PS 0 - 1 patients
  - 3 or 4: no
  - Not consistently prognostic and not commonly used: age, sex, sites of metastases, histology
- Patient preferences
  - 57% of patients would choose chemotherapy if 1-year survival increased by 10%
  - Of 81 patients previously treated with cisplatin-based chemotherapy, 68% receive chemotherapy if quality of life improved
Why Platinum-based Regimen?

- Guidelines from seven international organization recommended chemotherapy for stage IV NSCLC in patients with a PS of 0 – 1
  - 6 of 10 RCT of platinum-based chemotherapy vs. best supportive care (BSC) demonstrated a survival advantage with chemotherapy
- Four meta-analyses
  - Had variable inclusion criteria and endpoints
  - All demonstrated that receiving chemotherapy ↓ mortality relative to BSC
- Cisplatin = carboplatin
  - Cisplatin has ↑/↔ survival relative to carboplatin in two randomized trials
  - Less toxicity with carboplatin

Optimal Platinum-based Chemotherapy

- Doublet chemotherapy ↑ survival but ↑ toxicity over single agent chemotherapy
- Use platinum with third-generation chemotherapy (i.e., docetaxel, paclitaxel, gemcitabine, irinotecan, vinorelbine)
  - ↑ 1-yr survival relative to platinum with older agents (i.e., etoposide, ifosfamide, mitomycin C, vinblastine, vindesine)

Platinum-based Doublets

<table>
<thead>
<tr>
<th>Platinum</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>75–80 mg/m² IV day 1</td>
<td>Q 21-days</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m² (24-hr infusion) day 1 or 175 mg/m² (3-hr infusion) day 1</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC = 6 mg-hr/min day 1</td>
<td>Q21-days</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>225 mg/m² day 1</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m² day 1</td>
<td>Q 28-days</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25 mg/m²/week</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m² day 1</td>
<td>Q 28-days</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1,000 mg/m²/week</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m² day 1</td>
<td>Q 21-days</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75 mg/m² day 1</td>
<td></td>
</tr>
</tbody>
</table>
ECOG 1594:
Overall Survival by Treatment Group

Toxicity of First-line Doublet Chemotherapy
- Increased in PS=2 patients
- Mainly hematologic
  - Primarily ANC with severe neutropenia <10% and 0 – 4% death rates
  - In ECOG trial, worse with cisplatin/docetaxel
  - Anemia 7-30%
  - Thrombocytopenia: variable, in ECOG trial worse w/cis-gemcitabine
- Non-hematologic: nausea/vomiting, fatigue, alopecia, peripheral neuropathy (paclitaxel)

Advances in First-Line Treatment
- Triplet = doublet chemotherapy
- Adding vinorelbine to cisplatin/gemcitabine
- Adding irinotecan to carboplatin/paclitaxel
- Nonplatinum combinations have ↓ survival (not statistically significant), with ↓ toxicity in some trials
- In patients with stable or responsive disease chemotherapy should be discontinued after 3 or 4 cycles
  - toxicity increased if continue until progression
- Addition of targeted agents currently being studied
  - EGFR inhibitors added to standard chemotherapy of no-minimal benefit
  - Bevacizumab being evaluated
  - Bortezomib plus carboplatin/paclitaxel may be of benefit
  - Cannot use in those with squamous cell carcinoma because of hemoptysis
Second-line therapy

- **Docetaxel**
  - Two trials in comparing docetaxel to placebo OR vinorelbine OR ifosfamide in patients with prior platinum (prior paclitaxel allowed in one trial)
  - ↑ 1-year survival; response rate was <15%, stable disease 50%
  - Docetaxel 75 mg/m² IV q21 days
  - Similar efficacy, no clear toxicity benefit with weekly docetaxel

- **Pemetrexed**
  - Inhibits thymidylate synthase, dihydrofolate reductase
  - Equal efficacy but less toxicity to docetaxel in the second line setting (i.e., previous chemotherapy)
  - Vitamin B12 and folate status repletion ↓ risk of febrile neutropenia (by 10%) and grade ¾ neutropenia (by 34%)
  - Folate 100-300 µg PO QD, starting 1-2 week before and continuing 3 weeks after last pemetrexed dose
  - Vitamin 12 1 mg IM Q 9 weeks

Management of Metastases

- **Brain metastases**
  - Can present with any solid tumor, most frequent site of metastases in NSCLC
  - Presenting symptoms vary (e.g. headache, new onset nausea & vomiting)
  - Management depends on presence of solitary or multiple metastases
  - Treat with corticosteroids, radiotherapy, surgical resection, radiosurgery

- **Malignant Pleural Effusions**
  - Can occur with any solid tumors
  - Treated with talc slurry, or talc thoracoscopy

The ErbB Family and Ligands

- **EGF**
- **TGF-α**
- **Amphiregulin**
- **β-cellulin**
- **HB-EGF**
- **Epiregulin**
- **ErbB-1**
- **HER1**
- **EGFR**
- **ErbB-2**
- **HER2**
- **HER2 neu**
- **ErbB-3**
- **HER3**
- **ErbB-4**
- **HER4**

Tyrosine Kinase Domain

Extracellular

Intracellular
Activated Epidermal Growth Factor Receptor–Tyrosine Kinase (EGFR-TK)


EGFR Inhibitors

- Antibodies against erbB/family (EGFR, HER2)
  - Monoclonal, bispecific
  - FDA approved: Cetuximab
- Small molecule inhibitors of receptor tyrosine kinases (ERB family, EGFR, HER2, platelet derived growth factor)
  - gefitinib, erlotinib

Erlotinib Pharmacokinetics

- Pharmacokinetics
  - Bioavailability (150 mg) = 60% (100% with food)
  - Elimination half-life of 36 h (once-daily dosing)
  - Clearance not related to patient age, gender or body weight
    - 24% ↑ clearance in smokers
  - Hepatic elimination predominantly by CYP3A4, some CYP1A2
  - No PK data within hepatic impairment
  - No known clinically significant interaction or chemotherapy

- Use
  - 2nd or 3rd line setting
  - 150 mg vs. placebo (licensing): survival benefit
  - 1st line setting in combination with chemotherapy: no survival benefit
Adverse Effects with Erlotinib

- Pregnancy category D
- Most common:
  - Overall: rash 75%, diarrhea 54%, anorexia 52%, fatigue 52%, dyspnea 41%
  - Most grade 1 or 2
  - Grade 3/4: dyspnea and fatigue but rates similar to placebo control
- Rash
  - Acneform, mainly face or torso
  - Dose-related
  - Reversible
- Diarrhea: managed with loperamide
- Less frequent: conjunctivitis, transient elevations in liver function tests (hold), interstitial lung disease (hold if new or progressive onset of pulmonary symptoms such as dyspnea or cough)


Predictors of Response to EGFR Inhibitors

- Data conflicting, area of active research...some centers using for clinical care & may lead to cost saving measures
- EGFR expression
- Skin rash
- Pharmacogenomics
  - At least 18 different mutations reported
  - EGFR mutation rate varies by gender (20% women, 9% men), histology (21% adenocarcinoma, 2% other)
  - Mutations expressed more often in adenocarcinoma, women, Japanese and nonsmokers...which follows response pattern of EGFR tyrosine kinase inhibitors


Small Cell Lung Cancer

- Staging: VA Lung Group
  - Limited stage (LS)
    - disease confined to one hemithorax and regional lymph nodes encompassed with a tolerable radiotherapy port
  - Extensive stage (ES)
    - beyond these bounds
    - Common sites of metastases: contralateral mediastinal node, lung, bone, brain
SCLC: Prognostic Factors

- Stage of disease
- Patient factors
  - Performance status
  - Gender
- Laboratory values
  - Lactate dehydrogenase
  - Alkaline phosphotase
  - Sodium

SCLC: Treatment

- Median survival if untreated
  - 12 weeks for LS
  - 5 weeks for ES
- Surgery
  - Rare; upfront delays chemotherapy; after 5 cycles of CAV (cyclophosphamide/doxorubicin/vincristine) offers no survival benefit
- Radiotherapy
- Chemotherapy

Limited stage SCLC

- 50-80% response rate with 20-30% cure
- Cisplatin and etoposide (CE) has equal efficacy with less toxicity relative to CAV
- CE plus concurrent radiation therapy increased 2-3 year survival

Turrisi Oncology 1997; 9: 31 & Takada JCO 2002; 20: 3054
Prophylactic Cranial Irradiation (PCI)

- Brain metastases
  - 10-20% at diagnosis
  - Up to 70% subsequent risk of development in patients with LS
  - 9 of 11 trials show PCI reduces risk of brain metastases (16% vs 35%)
  - Most physicians recommend PCI for LS patients with CRs
  - Results in neurotoxicity in 19% of patients (range 10 - 86%)

Chest 1998; 113: S92

Extensive stage SCLC

- 50-80% response rate with few cures
- First line therapy
  - platinum-etoposide
  - Survival not improved by
    - ↑ dose intensity
    - Triplets (e.g., paclitaxel)
    - Alternating chemotherapy
    - Maintenance chemotherapy

Seminars in Oncology 1997; Supp 12: S12

- A separate US trial showed no survival benefit with cisplatin/irinotecan
  - Slight different in dosing, different pharmacogenetics?
- Third trial, mainly in US, being conducted

Noda NEJM 2002; 346:85-91; Hanna J Clin Oncol 2006
Second-line Therapy

- Response depends on magnitude and duration of response to first-line therapy
- Options
  - Oral etoposide
  - Topotecan

Schiller J Clin Onc 2001; 19: 2114