Treatment for Lung Cancer: Drug Therapy

Living in the Molecular Age: Advances Drug Therapy of Lung Cancer

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Non-small cell lung cancer: Stage at diagnosis

Types of Drug Therapy for Lung Cancer

• **Chemoprevention** - Drug treatment to reduce the risk of developing lung cancer in an “at risk” patient without cancer.
  • Retinoids (vitamin A analogs)- Unsuccessful.
  • Metformin (anti-diabetes drug)- Studies ongoing.

• **Adjuvant Chemotherapy** - Used after the initial treatment (usually surgery and/or radiation) to eliminate undetectable cancer cells that may be left behind.
  • High-risk stage I and stages II and III NSCLC

• **Neoadjuvant Chemotherapy** - Drugs used “upfront” sometimes with radiation before surgery.
  • Stage IIIA NSCLC, Pancoast’s tumors

• **Palliative Chemotherapy** - Drugs given to relieve lung cancer symptoms and maybe extend life, but are not for cure.
History of Drug Therapy for Lung Cancer

1960-70’s- First Generation- Alkylating agents, antimetabolites, antitumor antibiotics
  • Cyclophosphamide, CCNU, doxorubicin (Adriamycin®), 5-fluorouracil, methotrexate

1980’s- Second Generation- Multi-agent chemotherapy
  • Carboplatin, cisplatin, etoposide, mitomycin C, vinblastine

1990’s- Third Generation- Platinum-based doublets
  • Carboplatin, cisplatin, docetaxel (Taxotere®), gemcitabine (Gemzar®), paclitaxel (Taxol®), vinorelbine (Navelbine®)

2000’s- Fourth Generation- Targeted agents
  • Tyrosine kinase inhibitors: Gefitinib (Iressa®), erlotinib (Tarceva®), afatinib (Gilotrif®)
  • Monoclonal antibodies: Bevacizumab (Avastin®), cetuximab (Erbitux®)
  • Pemetrexed (Alimta®)

2010’s- Fifth Generation- Immunotherapy
  • Negative-immune checkpoint blockade
  • Cancer vaccines
Does chemotherapy cure or improve the survival of patients with lung cancer?
  • Answer: Yes, but it depends.

Does chemotherapy relieve symptoms associated with lung cancer?
  • Answer: Yes—sometimes.
## LACE Meta-analysis of Adjuvant Chemotherapy: Chemotherapy Benefit by Stage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths/No. Patients</th>
<th>HR for Overall 5-Yr. Survival (Chemotherapy vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>104/347</td>
<td>1.40 (0.95-2.06)*</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515/1371</td>
<td>0.93 (0.78-1.10)</td>
</tr>
<tr>
<td>Stage II</td>
<td>893/1616</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Stage III</td>
<td>878/1247</td>
<td>0.83 (0.72-0.94)</td>
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</tbody>
</table>

By the early 2000’s we had reached a plateau for cytotoxic chemotherapy in advanced NSCLC

ECOG 1594

- Cisplatin/paclitaxel
- Cisplatin/gemcitabine
- Cisplatin/docetaxel
- Carboplatin/paclitaxel

Platinum-doublet Chemotherapy in Advanced NSCLC

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Overall response</td>
<td>20-25%</td>
</tr>
<tr>
<td>Time-to-progression</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Median survival</td>
<td>8-9 months</td>
</tr>
<tr>
<td>1-year survival</td>
<td>20-25%</td>
</tr>
<tr>
<td>2-year survival</td>
<td>10-15%</td>
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</tbody>
</table>

Failed strategies:
- Triplet chemotherapy\(^2,3\)
- Non-platinum-based chemotherapy
- Single agent chemotherapy

Strategies to improve effectiveness of treatment

• **Better Treatments:**
  • Less toxic
  • More specific

• **Better Predictive Biomarkers:**
  • Which ones?

• **Better Patient Selection:**
  • What criteria?
Bevacizumab Blocks Angiogenesis

Recombinant humanized monoclonal antibody to VEGF-A

AVASTIN™ - VEGF complexes

NO BINDING

NO ANGIOGENESIS
Carbo/Taxol +/- Avastin: Key Clinical Outcomes

- Response rate: 15% for carbo/taxol vs. 35% for same chemo + avastin

**PFS**
- Carbo/taxol
- Carbo/taxol + avastin

\[ P < 0.001; \text{HR} = 0.86 \]
- Median PFS: 6.2 months vs. 4.5 months
- 6-Month PFS: 55% vs. 33%
- 1-Year PFS: 15% vs. 6%

**OS**
- Carbo/taxol
- Carbo/taxol + avastin

\[ P = 0.003; \text{HR} = 0.79 \]
- Median OS: 12.3 months vs. 10.3 months
- 1-Year OS: 51% vs. 44%
- 2-Year OS: 23% vs. 15%

HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Maintenance Chemotherapy for Lung Cancer

The continuation of reduced intensity chemotherapy to reduce the risk of tumor Progression in patients’ whose lung cancers have responded or remained stable when treated with initial standard chemotherapy.

- Pemetrexed (Alimta®)
- Bevacizumab (Avastin®)
- Erlotinib (Tarceva®)
The Molecular Age: Thymidylate synthetase (TS) expression in lung cancer

- SCLC – High TS
- Squamous – High TS
- Adeno – Low TS

Bhattacharjee, et al. PNAS. 2001
Selecting Chemotherapy by Molecular Analysis

Non-squamous* (n = 1252)

- Pemetrexed + cisplatin
  - HR = 0.844
  - (95% CI: 0.71–0.98)
  - \( p = 0.011 \)

- Gemcitabine + cisplatin

Squamous (n = 473)

- Pemetrexed + cisplatin
  - HR = 1.229
  - (95% CI: 1.00–1.51)
  - \( p = 0.051 \)

- Gemcitabine + cisplatin

*Non-squamous- adenocarcinoma, large cell carcinoma, and other/indeterminate histology.

“Driver mutations” in adenocarcinoma of the lung

Lung Adenocarcinomas
- Large Cell (10%)
- Adenocarcinoma (70%)
- Squamous Cell (20%)

NSCLC Heterogeneity
- KRAS (30%)
- Unknown (42%)
- EGFR (15%)
- EML4-ALK (5%)
- BRAF (2%)
- PIK3CA (1%)
- HER2 (2%)
- FGFR4 (2%)
- MEK (1%)

Harris T. Disc Med; 2010.
Inhibitors of Epidermal Growth Factor Receptor (EGFR)

afatinib, erlotinib, gefitinib
Effect of EGFR mutations on response to Tarceva®

- EGFR mutant: N = 9, Median > 15 months, 1-Year 89%
- EGFR wild-type: N = 34, Median 8.1 months, 1-Year 38%

Log-rank P = .012
• Exons #18, 19, 20 and 21 - tyrosine kinase domain.

• Deletions and missense mutations

• Allow drugs like Tarceva® to bind more tightly and inactivate EGFR

IPASS: Progression-Free Survival by EGFR Mutation Status

**EGFR mutation positive**

- Iressa (n=132)
- Carboplatin / paclitaxel (n=129)
- HR (95% CI) = 0.48 (0.36, 0.64)
- p<0.0001
- No. events gefitinib, 97 (73.5%)
- No. events C / P, 111 (86.0%)

**EGFR mutation negative**

- Iressa (n=91)
- Carboplatin / paclitaxel (n=85)
- HR (95% CI) = 2.85 (2.05, 3.98)
- p<0.0001
- No. events gefitinib, 88 (96.7%)
- No. events C / P, 70 (82.4%)

Treatment by subgroup interaction test, p<0.0001

**ITT population**

Cox analysis with covariates

Mok, ESMO 2008, A # LBA2
Targeted Agents for Treatment of Lung Cancer

- **EGFR overexpression (90%+)**
  - Cetuximab (Erbitux®)- Not approved for lung cancer in U.S.

- **EGFR sensitizing mutations (11-17%)**
  - Gefitinib (Iressa®), erlotinib (Tarceva®), afatinib (Gilotrif®)
  - T790M Resistance- Clovis COO-1686, AZD9291- Still investigational.

- **EML-4/ALK translocations and ROS-1 rearrangements (3-6%)**
  - Crizotinib (Xalkori®), ceritinib (Zykaydia®).

- **BRAF (V600E) mutations (1-4%)**
  - Vemurafenib (Zelboraf®), Debrafinib (Tafinlar®)- Not approved for lung cancer.

- **HER-2/neu overexpression (1-3%)**
  - Trastuzumab (Herceptin®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla®)- All not approved for lung cancer.
Immunotherapy of Lung Cancer: Negative Checkpoint Blockade
TergenpumatuCel-L

- Selected Lung Cancer Cell lines
- Insertion of α (1,3)GT Gene
- Expansion, irradiation and testing
- Production lots injected into Patients
Pre-HAL vaccination

64 Months Post-HAL vaccination
Eligibility and Randomization (1:1:1) (n = 480)

Docetaxel

Progression

Gemcitabine or Pemetrexed

Tergenpumautucel-L Q1 wk

Progression

Docetaxel or Gemcitabine or Pemetrexed with Tergenpumautucel-L Q1 wk

Tergenpumautucel-L Q2 wks

Docetaxel or Gemcitabine or Pemetrexed with Tergenpumautucel-L Q2 wks
Improvement in survival in patients with metastatic NSCLC over time

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Median Survival (months)</th>
<th>1-Yr. Survival (%)</th>
<th>2-Yr. Survival (%)</th>
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<tbody>
<tr>
<td>1980</td>
<td>4-6</td>
<td>10</td>
<td>3-5</td>
</tr>
<tr>
<td>2000</td>
<td>8</td>
<td>30-35</td>
<td>10-15</td>
</tr>
<tr>
<td>2014</td>
<td>12</td>
<td>50</td>
<td>20</td>
</tr>
</tbody>
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Cancer Deaths and NIH Research Spending (per Death)

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of Annual Deaths</th>
<th>NIH Research Spending ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>120,000</td>
<td>($6,812)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>40,000</td>
<td>($2,682)</td>
</tr>
<tr>
<td>Breast</td>
<td>10,000</td>
<td>($15,775)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>5,000</td>
<td>($5,294)</td>
</tr>
<tr>
<td>Lung</td>
<td>1,796,000</td>
<td>($1,796)</td>
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