Systemic Therapy of Non-small Cell Lung Cancer in the Older Adult

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Lung Cancer in Canada
Incidence, Mortality by Age

Incidence
- 1.4 million new cases, 1.2 million deaths per year
- 85% diagnosed with died of lung cancer
- Increased incidence with age
- Few older patients in trials
- Less organ reserve, more comorbidities, less willing to accept toxicity

Canadian Cancer Statistics 2008

Predictors of Chemotherapy Treatment

- 12,015 Stage IV NSCLC age >65 (SEER 91-96)
  - median age 73.5
  - men 60%, white 84%
  - comorbidities: 0-72%; 1-19%; 2+ 9%
- 73% referred to oncologist
- 26% received chemotherapy

Earle et al. J Clin Oncol 2002

Non-small Cell Lung Cancer (85%)
Treatment Strategies

Early Stage Locally Advanced Advanced
20% 25% 55%
Stage 1, 2 3A, 3B 3B, 4
Surgery Radiation Supportive Care
Adjuvant (IB-II) Chemotherapy +/- Surgery Systemic Therapy
(Radiation)
1. Platinum doublet
2. docetaxel, pemetrexed
2/3. erlotinib

Winton et al. NEJM 2004

NSCLC Treatment Strategies in Older Patients

Early Stage Locally Advanced Advanced
20% 25% 55%
Stage 1, 2 3A, 3B 3B, 4
Surgery Radiation Supportive Care
Adjuvant (IB-II) Chemotherapy +/- Surgery Systemic Therapy
(Radiation)
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Adjuvant Chemotherapy: NCIC CTG JBR.10 Vinorelbine/Cisplatin vs. Observation in Completely Resected IB, II NSCLC

69%
54%
HR 0.7, p = 0.02

Winton et al. NEJM 2004

Time (years)
NCIC CTG JBR.10: Chemotherapy Toxicity

- Patients ≤ 65 vs. >65 years

- No differences in:
  - G-CSF use
  - Hospitalizations
  - Treatment-related deaths

- Despite similar toxicities, older patients received significantly less chemotherapy
  - Fewer completed all treatment
  - 40% elderly vs. 56% young
  - More refused treatment
    - 40% elderly vs 23% young

Conclusions - Adjuvant Therapy

- Adjuvant cisplatin-based chemotherapy can be given safely to older patients, without increased toxicity
- Despite receiving less chemotherapy, older patients derive a significant survival benefit from adjuvant therapy
- Adjuvant chemotherapy should not be withheld on the basis of age alone
- Patients aged >75 require further study

LACE Meta-analysis: Effect of Age

- Pooled analysis of 4985 pts in 5 recent RCTs of cisplatin-based adjuvant chemotherapy
- Similar toxicity
- Older patients received less chemotherapy

Overall Survival

All Patients by Age Groups

Overall and Disease Specific Survival by Treatment Arm, Age >75

Survival by Treatment Arm:

Age >65

Age ≤65


Future of Adjuvant Therapy

• Less toxic treatment, better selection
• ANITA2 - vinorelbine vs. observation
• EGFR tyrosine kinase inhibitors
  - NCIC CTG BR.19 - adjuvant gefitinib x 2 yrs
  - RADIANT - adjuvant erlotinib x 2 yrs (EGFR+)

Chemotherapy in Advanced NSCLC in Older Adults

1. Single agent > supportive care
   - ELVIS 1 yr survival 32% v. 14%
2. GemVin = Gem or Vin alone (MILES)
3. Platinum doublet > single agent in fit pts
   - CALGB 9730 Med Survival PCb (8m) > P (5.8 m)
   - ECOG 1594, SWOG 9509, TAX 326
     * Similar benefit to younger but more toxicity
4. ≥80 years vs. 70 to 79 years
   * Significantly shorter survival with chemotherapy

Can we do better than chemotherapy?

VEGF Inhibitors in NSCLC

• Dramatic responses with tumor cavitation
• Side effects:
  • Bleeding (hemoptysis)
  • Hypertension
  • Proteinuria
  • Vascular events

Pivotal studies of Bevacizumab plus platinum-containing chemotherapy for NSCLC 1st line

E4599: Bevacizumab + Paclitaxel/Carboplatin improves OS

E4599 (US)

Bevacizumab 15mg/kg + CP (n=444)

Bevacizumab 7.5mg/kg + CP (n=444)

Placebo + CG (n=351)

Bevacizumab 15mg/kg† + CG (n=444)

Bevacizumab 7.5mg/kg† + CG (n=351)

Sandler, et al. NEJM 2006

AVAiL (Ex-US)

Previously untreated, stage IIIb, IV or recurrent non-squamous NSCLC (n=1,043)

E4599: Bevacizumab + Paclitaxel/Carboplatin improves OS

OS rate (%) 12 months 24 months

Bevacizumab + CP 51 23

CP 44 15

HR = 0.79 (95% CI: 0.67–0.92); p=0.003

Sandler, et al. NEJM 2006
AVAIL: Bevacizumab + Gemcitabine/Cisplatin prolongs PFS

PLACEBO

Avastin 15mg/kg TSG

Avastin 7.5mg/kg TSG

HR (95% CI)

0.82 (0.68 – 0.98)

0.75 (0.62 – 0.91)

p value

0.0391

0.0026

Median PFS (months)

6.1

6.5

6.7

E4599 Patients ≥70

N=224 (26%)

VEGF Inhibition in Older NSCLC patients

• Concern re toxicity, despite good PS
• Need careful selection, support
• Does VEGF inhibition accentuate vascular toxicity in older patients?
• VEGFR TKIs in development (cediranib, sunitinib, sorafenib, axitinib…)
• May have different safety issues

E4599 Gr 3/4 Toxicity ≥ 70

70+ yrs <70 p

Gr 4 neutropenia 34% 22% 0.02
GI bleed 3.5% 0.9% 0.005
Proteinuria 7.5% 1.3% 0.001
Motor Neuropathy 3.5% 0.6% 0.05
Related deaths 6.3% 2.6% 0.08
Grade 3-5 AEs 87% PCB vs. 61% PC (<0.001)

EGFR Tyrosine Kinase Inhibitors

• erlotinib, gefitinib
• oral, few side effects
• dramatic responses
  - nonsmokers, women, Asian, adeno histology
  - EGFR TK mutation, gene copy # (FISH), protein (IHC), k-ras mutation

Erlotinib (EGFR TKI) 2nd/3rd line after chemotherapy-failure

• Erlotinib improved
  - Response rate 8.9% v. <1% p<0.001
  - PFS 2.2 v. 1.8 months HR 0.61, p<0.001
  - OS 6.7 v. 4.7 months HR 0.70, p<0.001
• Quality of Life

Erlotinib Study - Response

February 28, 2002

June 6, 2002

A Comparison of PFS by Treatment Arm in Young and Elderly patients

Young <70
HR 0.64 (CI 0.53-0.76), p<0.0001
Median: Placebo – 1.8 months
Erlotinib – 2.1 months

Elderly ≥70
HR 0.63 (CI 0.44-0.90), p=0.009
Median: Placebo – 2.1 months
Erlotinib – 3.0 months

A Comparison of OS by Treatment Arm in Young and Elderly patients

Young <70
HR 0.73 (CI 0.61-0.89), p=0.001
Median: Placebo – 4.7 months
Erlotinib – 6.4 months

Elderly ≥70
HR 0.92 (CI 0.64-1.34), p=0.67
Median: Placebo – 5.0 months
Erlotinib – 7.6 months

Treatment after Progression on BR.21

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Young</th>
<th>Elderly</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>21%</td>
<td>13%</td>
<td>0.04</td>
</tr>
<tr>
<td>EGFR inhibitor</td>
<td>3%</td>
<td>4%</td>
<td>0.6</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>21%</td>
<td>14%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Wheatley-Price et al. Proc ASCO 2008

Selected Treatment-Related Toxicities by Age (Erlotinib Arm only)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Young (n=373)</th>
<th>Elderly (n=112)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>83%</td>
<td>18%</td>
<td>88%</td>
</tr>
<tr>
<td>Rash</td>
<td>72%</td>
<td>14%</td>
<td>75%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14%</td>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13%</td>
<td>&lt;1%</td>
<td>19%</td>
</tr>
</tbody>
</table>

* Older patients more likely to stop (12% v 3%) or interrupt, received slightly less erlotinib overall

Conclusions - 2nd/3rd line EGFR TKI

- The benefit of erlotinib is not restricted to young patients
- Nonsignificant survival benefit in older patients may be related to small numbers, less subsequent chemotherapy
- Some caution in older patients required as:
  - Toxicity higher although still uncommon

Wheatley-Price et al. Proc ASCO 2008
**INVITE Study Design**

- **Phase II (open-label)**
- **Stage III/IV NSCLC**
- **Chemonaive**
- **≥70 years**
- **WHO PS 0-2**
- **Tumor tissue collection mandatory**

**Primary endpoint:**
- Progression-free survival (PFS)

**Secondary endpoints:**
- Overall survival
- Response rate (RECIST)
- Quality of life
- Pulmonary symptom improvement
- Safety

**Exploratory endpoints:**
- EGFR biomarkers

**Gefitinib**
- 250 mg/day
- 1:1 randomization

**Vinorelbine**
- 30 mg/m² on Days 1 & 8 of 21-day cycle
- (n=99)

NSCLC, non-small-cell lung cancer; WHO, World Health Organization; PS, performance status; EGFR, epidermal growth factor receptor; RECIST, Response Evaluation Criteria in Solid Tumors

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**INVITE Progression-Free Survival**

- HR = 1.19
- 90% CI: 0.90 to 1.66
- 95% CI: 0.65 to 1.65
- P = .310; n = 196; events = 156

RR 3% v. 5%

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**INVITE Study Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (N=97)</th>
<th>Vinorelbine (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at risk</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>0-12</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>13-24</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>25-36</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>37-48</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>49-60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR=0.98 (95% CI 0.66, 1.47)

n=196; 103 deaths

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**Overall Survival by EGFR gene copy number (FISH)**

**EGFR FISH +ve**

**EGFR FISH -ve**

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**Quality of Life**

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<tr>
<th></th>
<th>Gefitinib</th>
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<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Rash</td>
<td>2.1%</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2.1%</td>
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<td>0</td>
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% Improvement over Baseline

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Grade ≥3 Adverse Events

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Can we abandon 1st line chemotherapy for EGFR TKIs?

- Not yet - risk of inferior efficacy
- EGFR TKIs are less toxic, with better QL improvement in phase II study
- Larger studies are required, ideally with molecular or clinical selection

Palliative Treatment Options

1. Fit
   - Platinum-based
   - Single agent
   - EGFR inhibitors
   - Optimize comorbidities
   - Supportive Care

2. In Between
   - Optimize comorbidities
   - Supportive Care

3. Frail
   - ?
   - Optimize comorbidities
   - Supportive Care

Treatment Options

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   - ?
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Conclusions

- Older patients benefit from systemic lung cancer therapy, including adjuvant chemotherapy
- In palliative setting, platinum-based combinations, single agent, EGFR TKIs all options tolerable, beneficial
- Caution still required, especially in >80 population
- Optimize comorbidities, supportive interventions