New (Data on) Adjuvant Chemotherapy for NSCLC

Cardiothoracic Surgery Update
Siam City Hotel, 17 Jan 2010

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Medical Oncology Unit,
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Topic Outline

- Background
- Recent trials of adjuvant chemotherapy
- Biomarker for treatment benefit/response
- New: targeted drug as potential adjuvant agent
Roles of Chemotherapy as an Adjuvant Rx in Resected Early Stage NSCLC

Expert Consensus 1990

Considered “experimental”

Never been sufficient evidences to support its use

Lung cancer 1991: 7; 11-13
Adjuvant Chemotherapy
1995 Meta-analysis (n 1394)

- 8 trials
- cisplatin-based

- Marginal improvement in 5-yr survival

- Absolute benefit = 5%
- p 0.08

Two Decades of Progress in Advance NSCLC Drug Treatment

- 1900: Nihilistic era
  - 1995: 1st targeted drug (gefitinib, erlotinib)
  - 2000: Survival improves
  - 2005: More targeted Rx combined with chemoRx
  - 2007: Four 3rd generation chemoRx available

Survival improves
## RECENT ADJUVANT TRIALS OF CHEMOTHERAPY IN RESECTED NSCLC

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>CT regimen</th>
<th>n</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2nd generation drug combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INT 0115</td>
<td>USA</td>
<td>4 x VP16-P</td>
<td>462</td>
<td>Completed</td>
</tr>
<tr>
<td>ALPI-EORTC</td>
<td>Italy/Europe</td>
<td>3 x MVP</td>
<td>1197</td>
<td>Completed</td>
</tr>
<tr>
<td>IALT</td>
<td>Int&lt;sup&gt;nal&lt;/sup&gt;</td>
<td>3/4 x V-P/ NVB</td>
<td>1867</td>
<td>Completed</td>
</tr>
<tr>
<td>BLT</td>
<td>Int&lt;sup&gt;nal&lt;/sup&gt;</td>
<td>3 x V-P</td>
<td>481</td>
<td>Completed</td>
</tr>
<tr>
<td><strong>3rd generation drug combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCI-C</td>
<td>Canada+USA</td>
<td>4 x NVB-P</td>
<td>482</td>
<td>Completed</td>
</tr>
<tr>
<td>ANITA 01</td>
<td>Int&lt;sup&gt;nal&lt;/sup&gt;</td>
<td>4 x NVP-P</td>
<td>831</td>
<td>Completed</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>USA</td>
<td>4 x Taxol-Carbo</td>
<td>504</td>
<td>Completed</td>
</tr>
</tbody>
</table>
Should we use adjuvant chemotherapy in patients with resected NSCLC?
## Recent (-) Trials of Adjuvant CT in Completely Resected NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>CT Regimen</th>
<th># of Patients</th>
<th>Outcome on OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT 0115 (XRT)</td>
<td>USA</td>
<td>VP16-P x 4</td>
<td>462</td>
<td>Negative</td>
</tr>
<tr>
<td>ALPI/EORTC</td>
<td>Italy/Europe</td>
<td>MVP x 3</td>
<td>1197</td>
<td>Negative</td>
</tr>
<tr>
<td>BLT</td>
<td>International</td>
<td>V-P x 4</td>
<td>481</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**ALPI**: large trial, negative result
- use of 3 drug-combination
- toxic

The First Positive Large Trial = International Adjuvant Lung Cancer trial (IALT)

Stage I-III NSCLC Complete resection

N 1867

Cisplation plus
• VP 16 or x 4 cycles
• Vinorelbine or
• Vinblastine, vincristine

Observation

RT is optional

Arrigada, et al. NEJM 2004
Le Chavalier. ASCO 2008
IALT—Overall Survival
(56 months follow-up)

HR = 0.86 [0.76-0.98] P<.03

5-yr survival
Sx+CT 44.5%
Sx 40%

2005: Paradigm Shifted Further

Recently Completed (+) Randomized Adjuvant Trials in Early-Stage NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB</td>
<td>II-IIIA</td>
<td>Carboplatin/paclitaxel</td>
</tr>
<tr>
<td>NCI-C</td>
<td>II-IIIA</td>
<td>Cisplatin/vinorelbine</td>
</tr>
<tr>
<td>ANITA</td>
<td>I-IIIA</td>
<td>Cisplatin/vinorelbine</td>
</tr>
</tbody>
</table>

1B+2: vinorelbine vs nil
- Absolute benefit in 5-yr survival: 15% (p 0.002)
- Median survival: 73 vs 94 months
- HR 0.69 (p 0.012)

1B: paclitaxel vs none
- Absolute benefit: 12% @ 4 yr
- HR 0.62 (p 0.028)
ANITA Trial (N= 840, I-III) 
cis-vinorelbine vs no chemoRx

Overall Survival- ITT

- HR 0.8 (0.66-0.96)
- P 0.017

Median survival
- Obs 43.7%
- NVB 65.7%
- stage IB→ no benefit

Short course adjuvant chemoRx has emerged as "standard" practice in resected stage Ib-III.

Evolution of Adjuvant Chemotherapy in NSCLC

- **1995 Meta-analysis**: HR 0.87, p=0.08
- **2005 IALT - Overall Survival**: HR = 0.86 [0.76-0.98], p<0.03
- **2005**: HR 0.62, P=0.028

Survival Time (Months)

- 4 years: 71%
- 5 years: 59%
- 6 years: 69%
- 7 years: 54%

Note: HR stands for Hazard Ratio, and P values indicate statistical significance.
2006-2009 Updates

- No new major trials
- LACE meta-analysis \(\rightarrow\) confirms benefit of adjuvant cisplatin-based chemoRX

**Surprise:** 2/4 of previously +ve trials became non-significant with longer F/U
- CALGB9633: stage IB Rx’ed w/ Taxol-carboplatin
- IALT: largest trial to date, only disease-free survival benefit remains (2008)

- **NCIC JBR10:** cis-vinorelbine \(\rightarrow\) still going strong > 9 yr F/U
IALT—Overall Survival
(56 months follow-up)

5-yr survival
Sx+CT 44.5%
Sx 40%

HR = 0.86 [0.76-0.98]  P<.03

At risk
0 1 2 3 4 5
932 775 624 450 308 181
935 774 602 432 286 164

IALT: Cisplatin + a Vinca or Etoposide
2008 Update: 7.5-Year Median Follow-Up

Chemotherapy: 578 deaths
- 495 deaths before 5 years
- 83 deaths after 5 years

Mostly non-cancer Related death

Early-Stage NSCLC

Long-Term Follow-Up IALT: DFS

Long Term F/U (9 years) of JBR 10 (Canadian cis-Vinorelbine)

1st Report 2005, NEJM
Absolute improvement 15%

Update ASCO 2009
Absolute improvement 11%
Should we use adjuvant chemotherapy in patients with resected NSCLC?
LACE Meta-Analysis (N=4584) Survival by Trial

Median F/U 5.1 yrs
SCC 49%, ADC 39%
IA 8%, IB 30%, II 35%, III 27%

## Stage-Specific Hazard Ratios

### Recent Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>IB</th>
<th>II</th>
<th>IIIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>0.95</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td>JBR.10</td>
<td>0.94</td>
<td>0.59</td>
<td>N/A</td>
</tr>
<tr>
<td>ANITA</td>
<td>1.10</td>
<td>0.71</td>
<td>0.69</td>
</tr>
<tr>
<td>CALGB</td>
<td>0.8</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>JCOG (UFT)</td>
<td>0.48</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Legend:**
- Negative
- Positive
- Indeterminate
New Era of Cancer Medicine

Biomarkers
Prognostic and Predictive

ERCC1

Repair DNA damage from cisplatin
ERCC1-Negative: Overall Survival

Adjusted HR = 0.65, 95% CI [0.50-0.86], P = .002

ERCC1-Positive: Overall Survival

Adjusted HR = 1.14, 95% CI [0.84-1.55], P = .40

## Prospective Biomarker Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Therapy</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 30506</td>
<td>Stage I</td>
<td>+/- Chemotherapy</td>
<td>Metagene</td>
</tr>
<tr>
<td>ITACA</td>
<td>Stage I-III A</td>
<td>Cisplatin/pemetrexed</td>
<td>ERCC1/TS</td>
</tr>
<tr>
<td>TASTE</td>
<td>Stage I-III A</td>
<td>Cisplatin/pemetrexed or erlotinib</td>
<td>ERCC1/ EGFR mut</td>
</tr>
</tbody>
</table>
Targeted Therapy Trials in Adjuvant Setting

- Attractive approach
- At least 4 targeted drugs with data showing improvement in survival of pts with metastatic NSCLC

- Erlotinib, gefitinib : EGFR TKI
- Bevacizumab : Anti-VEGF Ab
- Cetuximab: Anti-EGFR Ab
# Phase III “Targeted” Therapy Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Therapy</th>
<th>Target</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1505¹</td>
<td>IB(≥4cm) -IIIA</td>
<td>Chemo +/- bevacizumab</td>
<td>Wish we knew</td>
<td>1500 OS</td>
</tr>
<tr>
<td>RADIANT²</td>
<td>I-IIIA</td>
<td>Erlotinib x 2 years</td>
<td>EGFR-IHC+</td>
<td>945 DFS</td>
</tr>
<tr>
<td>MAGRIT³</td>
<td>IB-IIIA</td>
<td>Vaccine x 27 months</td>
<td>MAGE-A3</td>
<td>2270 DFS</td>
</tr>
</tbody>
</table>

Conclusion
Systemic Therapy for Resected NSCLC

- Meaningful improvement in survival with short course cisplatin-based regime (3rd gen. drug preferred)
- Consistent benefit in stage II-III
- Stage IB: only large tumor >4 cm appear to benefit in subgroup analysis
- Future trend: biomarker driven decision
  - ERCC, EFGR mutation, etc
  - Role of targeted drug under investigation
The End
Back up
The effect of **cisplatin + vinorelbine** was marginally better than the effect of other drug combinations; this is significant when the other combinations are pooled ($P = .04$, *post hoc* analysis)

CT Effect & Stage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>102 / 347</td>
<td></td>
<td>1.41 [0.96; 2.09]</td>
</tr>
<tr>
<td>Stage IB</td>
<td>509 / 1371</td>
<td></td>
<td>0.92 [0.78; 1.10]</td>
</tr>
<tr>
<td>Stage II</td>
<td>880 / 1616</td>
<td></td>
<td>0.83 [0.73; 0.95]</td>
</tr>
<tr>
<td>Stage III</td>
<td>865 / 1247</td>
<td></td>
<td>0.83 [0.73; 0.95]</td>
</tr>
</tbody>
</table>

Test for trend: p = 0.051

CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin + vinorelbine (13% of stage IA patients versus ~43% for other stages)

Early-Stage NSCLC → Perspective with ANITA

IALT: Results of ERCC1 Analysis

- Overall positivity = 44% (H-score >1.0)
- Significant correlation of ERCC1 expression seen with age (lower in younger patients), histologic subtype (lower in adenocarcinoma), and pleural invasion (lower if no pleural invasion)

**Predictive Adjusted Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Chemo (N = 389)</th>
<th>Control (N = 372)</th>
<th>HR/ P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 neg (N = 426)</td>
<td>47%</td>
<td>39%</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>56 months</td>
<td>42 months</td>
<td>.002</td>
</tr>
<tr>
<td>ERCC1 pos (N = 335)</td>
<td>40%</td>
<td>46%</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>50 months</td>
<td>55 months</td>
<td>.40</td>
</tr>
</tbody>
</table>

An Opportunity to Utilize Improved Prognosis

CALGB 30506
D. Harpole, PI

[Diagram showing flow of Stage IA NSCLC Patients through surgery, gene expression analysis, lung metagene predictor, and consequent decisions for observation or randomization to chemotherapy or observation, with statistical significance indicated.

Protocol schema is currently under revision]
TASTE Design

Control Arm
Cisplatin-pemetrexed

Experimental Arm Customized

EGFR mutated
Erlotinib

ERCC1+
Observation

EGFR wildtype

ERCC1-
Cisplatin-pemetrexed

Non-SCC NSCLC stage II and IIIA (non-N2)