Adjuvant and Neoadjuvant Chemotherapy in NSCLC: a Paradigm Shift

Fadi Sami Farhat, MD
Hematology Oncology

drfadi@drfadi.org
First Choice of Therapy: Surgery

Mountain CF, Chest, 1997, 111, 1710
The Problems?

- 40-60% of patients with radically resected NSCLC will develop distant metastases\(^1\)

- Cancer cells present in bone marrow of >30% of resectable NSCLC patients\(^2\)
  - correlated with shorter survival

Can we eliminate micrometastases with additional chemotherapy?

\(^1\)Yasumoto et al., 2003, *Ann Thorac Surg* 76, 194.
Meta-Analysis on Role of CT in NSCLC

Absolute survival benefit with cisplatin-containing regimens

- Trend: CT additive to surgery
- No benefit with RT

### Early Randomized Trials of Adjuvant CT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pt. Population (Stage)</th>
<th>No. pts</th>
<th>CT Regimen</th>
<th>Absolute Benefit in OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLT (2003)</td>
<td>Early-stage</td>
<td>381</td>
<td>Cis-based x 3</td>
<td>No benefit</td>
</tr>
<tr>
<td>ALPI (2003)</td>
<td>I, II, IIIA</td>
<td>1209</td>
<td>MVP</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Lack of benefit in early trials:

- Poor compliance of chemotherapy:
  - Br Med J 1995 meta-analysis: RDI < 65%
- Possible explanations:
  - Post-thoracotomy patients have insufficient PS for CT?
  - Centers uncomfortable with CT?
Randomized Trials of Adjuvant CT
Starting to see a benefit ...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pt. Population (Stage)</th>
<th>No. pts</th>
<th>CT Regimen</th>
<th>Absolute Benefit in OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLT (2003)</td>
<td>Early-stage</td>
<td>381</td>
<td>Cis-based x 3 adjuvant</td>
<td>No benefit</td>
</tr>
<tr>
<td>ALPI (2003)</td>
<td>I, II, IIIA</td>
<td>1209</td>
<td>MVP</td>
<td>No benefit</td>
</tr>
<tr>
<td>JLCRG (2004)</td>
<td>I</td>
<td>979</td>
<td>UFT</td>
<td>3% (5-y)</td>
</tr>
<tr>
<td>Japan meta-analysis (2004)</td>
<td>Early-stage</td>
<td>2003</td>
<td>UFT</td>
<td>5% (5-y) 7% (7-y)</td>
</tr>
<tr>
<td>IALT (2004)</td>
<td>I-III</td>
<td>1867</td>
<td>Cis-based x 3-4</td>
<td>4% (5-y)</td>
</tr>
</tbody>
</table>
Meta-Analysis: OS with Adjuvant CT vs. Surgery Alone

Problems with Adjuvant CT

- Low compliance: ≤ 85% identification of the best CT combination
- High risk of local relapse despite radical resection
- Growth factors released during and after surgery may stimulate residual cancer cells
- Putative risk of seeding of cancer cells during surgery

Can neoadjuvant CT solve some of these problems?
Could Neoadjuvant Administration be the Answer?

- Current body of evidence neoadjuvant chemotherapy (1987-2005):
  - >40 trials; >2000 patients
  - Feasible with response rates leading to resection: 30-80%; Median OS: 13-32 months

- Differentiators with adjuvant chemotherapy
  - Positive:
    - Better tolerated, better compliance
    - Theoretically results in more radical resections with less distant mets
    - Treats distant mets at earliest possible time
    - Patient selection (PD do not benefit from therapy)
  - Negative:
    - Delays surgery
    - Staging is clinical: less accurate than pathological (true pathological staging unknown)
Taxotere as Neoadjuvant Therapy: International Multicenter Phase III Trial

N = 274
Stage IIIA and IIIB

Randomize

N = 274
Stage IIIA and IIIB

Randomize

Taxotere 100 mg/m$^2$ before
local therapy: RT or surgery
(n = 134: IIIA 65% (N2 43%,
T3 22%), IIIB 35%)

Local therapy: RT or surgery
(n = 140: IIIA 69% (N2 46%,
T3 23%), IIIB 31%)

## Neoadjuvant Taxotere Phase III Trial: Results

<table>
<thead>
<tr>
<th></th>
<th>Taxotere (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (months, 95%, CI)</td>
<td>14.8 (12.2-16.7)</td>
<td>12.6 (9.7-16.0)</td>
</tr>
<tr>
<td>Median survival by disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA N2</td>
<td>15.7</td>
<td>15.5</td>
</tr>
<tr>
<td>IIIA T3</td>
<td>17.4</td>
<td>13.6</td>
</tr>
<tr>
<td>IIIB</td>
<td>12.8</td>
<td>9.0</td>
</tr>
<tr>
<td>One-year survival</td>
<td>59%</td>
<td>51%</td>
</tr>
<tr>
<td>Median time to progression, mo</td>
<td>9.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Response rate</td>
<td>28%</td>
<td>-</td>
</tr>
</tbody>
</table>

Neoadjuvant Taxotere
JCOG 0204 Trial

- Randomize
  - NSCLC c-stage IB-II medically fit for curative operation
  - Stratified for institution stage (IB vs II)

- Treatment:
  - CDDP 80 mg/m² d 1 Taxotere 60 mg/m² d 1 q 4 wk x 2 courses (TP)
  - Taxotere 70 mg/m² d 1 q 3 wk x 3 courses (T)

- Surgery

# Neoadjuvant Taxotere: JCOG Results

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed CT</td>
<td>38/40 (95%)</td>
<td>24/39 (62%)</td>
</tr>
<tr>
<td>ORR to CT</td>
<td>18/40 (45%)</td>
<td>6/39 (15%)</td>
</tr>
<tr>
<td>Resection</td>
<td>39/40 (98%)</td>
<td>34/39 (87%)</td>
</tr>
<tr>
<td>Complete resection</td>
<td>38/40 (95%)</td>
<td>33/39 (85%)</td>
</tr>
<tr>
<td>Pathologic CR</td>
<td>2/40 (5%)</td>
<td>0/39 (0%)</td>
</tr>
<tr>
<td>DFS at 1 year</td>
<td>77%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Phase II Swiss Trial of Neoadjuvant Taxotere-Cisplatin: Study Design

**Patients:** mediastinoscopically staged NSCLC IIIA pN2

**Chemotherapy**

- Cisplatin: 80-100 mg/m²
- Taxotere: 85 mg/m²

**Chemotherapy**

- x 3 courses

**Surgery**

- if tumor reaches resection margin
- involvement of the uppermost mediastinal lymph node

**Off-study**

- PD
- NC, PR, CR

- day 64

**Radiotherapy**

- if tumor reaches resection margin
- involvement of the uppermost mediastinal lymph node

Swiss Phase II Trial: Treatment

Patients who received 3 cycles: 86/90
Number of cycles administered: 265 cycles

Actual dose intensity:
- Taxotere: 84.7 (53-96) mg/m²
- Cisplatin:
  - level 1: 79.5 (40-94) mg/m²
  - level 2: 98.4 (0-104) mg/m²

Deaths on therapy:
- CNS metastasis (cycle 2): 1 pt
- Gastric bleeding (on steroids) (cycle 1): 1 pt

Swiss Trial: Responses

- PR: 58%
- CR: 8%
- PD: 10%
- NC: 24%

## Betticher et al, Results Relative to BLOT Phase II Trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Betticher et al (BLOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant regimen</td>
<td>Cisplatin + Taxotere</td>
</tr>
<tr>
<td></td>
<td>Carboplatin + paclitaxel</td>
</tr>
<tr>
<td>No. of pts receiving 3 cycles</td>
<td>86/90</td>
</tr>
<tr>
<td></td>
<td>40/134</td>
</tr>
<tr>
<td>Patient population</td>
<td>IIIA</td>
</tr>
<tr>
<td></td>
<td>IB-IIIA</td>
</tr>
<tr>
<td>ORR, %</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

Swiss Trial: Resection

- 78 patients (87%) underwent surgery

- Downstaging
  - With N0 and N1 at surgery was seen in 31% and 29% of patients, respectively
  - Was associated with pathologic response ($P = .011$)

- Radiotherapy was given to 33 patients
  - Mainly for involvement of the upper mediastinal lymph node

Complete resection was feasible in 48% and 55% of patients included and patients operated, respectively.

Swiss Trial: Risk of Relapse at 5 Years

75 patients resected

- 14/75 (19%) Local relapse
- 26/75 (35%) Distant mets
- 8/75 (11%) Local and distant

Without relapse: 27/75 (36%)
New Phase III Trial: SAKK 16/00

Patients: CBNPC stage IIIA, pN2 by mediastinoscopy

Chemotherapy
- Cisplatin: 100 mg/m²
- Taxotere: 85 mg/m²

Surgery

Radiotherapy

Randomize

3 cycles chemotherapy (Taxotere/Cisplatin) -> Surgery

3 cycles chemotherapy (Taxotere/Cisplatin) -> Radiotherapy -> Surgery
Swiss Trial Complete Resection and Survival

Overall survival

Complete resection

Incomplete resection

P < .0001

Swiss Trial N0-N1-N2 Downstaging and Survival

Overall survival

- pN0
- pN1
- pN2

$P = .096$

$P = .016$

Swiss Trial N0/N1 Downstaging and Survival

Overall survival

pN0/1

pN2

P < .0001

Conclusions: Neoadjuvant Chemotherapy in Stage IIIA NSCLC

Neoadjuvant Cisplatin + Taxotere:

- Is well tolerated
- Does not increase perioperative morbidity and mortality
- Increases survival, reduces the risk of distant and local relapse if the chemotherapy is active on the:
  - primary tumor (60-90% necrosis/fibrosis)
  - mediastinal lymph nodes (clearance)
Conclusions: Adj. and Neoadj. Chemotherapy for Resectable NSCLC

- **Adjuvant chemotherapy**
  - Increasing evidence
  - Emerging standard of care for early-stage disease (stage II)

- **Neoadjuvant chemotherapy**
  - Optimal role, patient populations, regimens, combinations, and modalities continue to be investigated
Awaited Phase III Neoadjuvant Trials

- **NATCH:**
  - N=600 Stage IB, II, IIIA (T3N1)
  - Adjuvant vs. neoadjuvant paclitaxel-carboplatin
  - Results expected 2006-07

- **Belani et al:**
  - N=354 Stage I, II and IIIA (N0-1)
  - Adjuvant vs. neoadjuvant Taxotere-cisplatin
  - Primary endpoint comparative dose intensity