Treatment of advanced NSCLC in the elderly

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Most cancer patients are aged >65 years

More than 40% of lung cancer patients are over 70 years old.
Cardiovascular / pulmonary co-morbidities and lung cancer linked to tobacco smoking

Disease prevalence in the elderly

Organ function declines with age

- **Cardiovascular function**¹
  - Decreased elasticity of arterial system
  - Loss of myocytes and atrial pacemaker cells
  - Increased fibrosis of cardiac fibrous skeleton

- **Renal function**²
  - Decreased renal blood flow
  - Decreased glomerular filtration rate
  - Decreased creatinine clearance

- **Hepatic function**³
  - Reduced hepatic blood flow
  - Decline in cytochrome P450 system

- **Bone Marrow function**⁴
  - Reduction of hematopoietic reserve

Domains of geriatric assessment

CHRONOLOGICAL vs. BIOLOGICAL AGE

- **Function**
  - Performance status (PS)
  - Activities of daily living (ADL)
  - Instrumental activities of daily living (IADL)
  - Advanced activities of daily living (AADL)

- **Comorbidity**
  - Comorbidity scales (Charlson; CIRS)

- **QoL**
  - Disease-specific questionnaires

- **Cognition**
  - Folstein Minimental Status

- **Emotions**
  - Geriatric Depression Scale (GDS)

- **Social support network**
- **Polypharmacy**
- **Nutrition**
A systematic review analyzed 73 studies on geriatric assessment in cancer patients.

The analysis showed that the assessment is feasible.

There is limited evidence that it impacted treatment decision making.

Further research examining the effectiveness of geriatric assessment on treatment decision and outcome is needed.

Treatment of Advanced Non–Small-Cell Lung Cancer in the Elderly: From Best Supportive Care to the Combination of Platin-Based Chemotherapy and Targeted Therapies

Cesare Gridelli, Division of Medical Oncology, “S.G. Moscati” Hospital, Avellino, Italy
Overall survival

Log-rank test: P=0.03
Cox model: P=0.02

Vinorelbine
MS = 6.5 months

Supportive care
MS = 4.8 months

EORTC LC-13: QoL analysis

Estimated effect of vinorelbine with 95% CI

Dyspnea
Cough
Hemoptysis
Sore mouth
Swallowing troub.
Neuropathy
Hair loss
Pain in chest
Pain in shoulder
Pain elsewhere
Analgesics

Gridelli et al. J Natl Cancer Inst, 1999

Vinorelbine vs. docetaxel trial

- A phase III randomized trial comparing vinorelbine versus docetaxel showed no statistically significant difference in terms of survival.

- Response rate and progression free survival were superior in docetaxel arm (22.9% and 7%; 5.4 and 3.1 months).

MILES Study

Vinorelbine
30 mg/m²
D1, D8

Gemcitabine
1200 mg/m²
D1, D8

Gemcitabine + Vinorelbine
NVB: 25 mg/m²
D1, D8
Gem: 1000 mg/m²
D1, D8

Retrospective analyses of elderly patients outcomes in large randomized trials

- Several retrospective analyses of elderly patients included in large phase III randomized trial without upper limit age have been performed.

- The analyses showed that platin-based chemotherapy is feasible in the elderly population with the same outcomes observed in their younger counterpart but with increased toxicity.

- These analyses are at high risk of selection bias.
Retrospective analyses of phase III trials on advanced NSCLC elderly patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Group</th>
<th>Trial No.</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer, 2000</td>
<td>ECOG</td>
<td>5592</td>
<td>PE vs PTax vs PTax+G-CSF</td>
</tr>
<tr>
<td>Kelly, 2001</td>
<td>SWOG</td>
<td>9308-9509</td>
<td>P vs PV/ PV vs CbTax</td>
</tr>
<tr>
<td>Lilienbaum, 2002</td>
<td>CALGB</td>
<td>9730</td>
<td>Tax vs CbTax</td>
</tr>
<tr>
<td>Langer, 2003</td>
<td>ECOG</td>
<td>1594</td>
<td>PTax vs CbTax vs PG vs PTxt</td>
</tr>
<tr>
<td>Fossella, 2003</td>
<td>TAX</td>
<td>326</td>
<td>PV vs PTxt vs CbTxt</td>
</tr>
</tbody>
</table>
Phase II studies of cisplatin-based chemotherapy in advanced NSCLC patients

- Several phase II studies of cisplatin-based regimens using attenuated doses of drugs or special weekly schedules have been performed.
- Interesting results and feasible toxicity profiles have been observed.
- The results need to be confirmed in large phase III randomized trials.
Cisplatin-based chemotherapy with special doses or schedule in advanced NSCLC elderly patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>N.Pts</th>
<th>% OR</th>
<th>MS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feliu, 03</td>
<td>CDDP+GEM*</td>
<td>46</td>
<td>35</td>
<td>10.2</td>
</tr>
<tr>
<td>Lippe, 00</td>
<td>CDDP+GEM**</td>
<td>15</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Berardi, 03</td>
<td>CDDP+GEM***</td>
<td>48</td>
<td>31.8</td>
<td>9</td>
</tr>
<tr>
<td>Mattioli, 02</td>
<td>CDDP+VNR***</td>
<td>33</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Ohe, 04</td>
<td>CDDP+TXT***</td>
<td>33</td>
<td>52</td>
<td>15.8</td>
</tr>
<tr>
<td>Feliu, 08</td>
<td>CDDP+TXT*</td>
<td>42</td>
<td>31</td>
<td>8.9</td>
</tr>
<tr>
<td>Gridelli, 08°</td>
<td>CDDP+VNR#</td>
<td>61</td>
<td>36</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>vs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP+GEM§</td>
<td>60</td>
<td>43</td>
<td>10.9</td>
</tr>
</tbody>
</table>

°Phase II randomized trial; *CDDP 50 mg/m² Q21; **CDDP 35 mg/m² weekly; ***CDDP 25 mg/m² weekly; #CDDP 40 mg/m² Q21; §CDDP 60 mg/m² Q21
Cisplatin Plus Gemcitabine or Vinorelbine for Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The MILES-2P Studies


Purpose
Two phase II trials were done to evaluate the feasibility of cisplatin combined with gemcitabine or vinorelbine in elderly patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with advanced NSCLC who were older than 70 years of age and who had a performance status of 0 to 1 were eligible. Cisplatin was given on day 1 (a starting dose of 50 mg/m² with increasing increments of 10 mg/m² at each level) and gemcitabine (1,000 mg/m²) or vinorelbine (25 mg/m²) on days 1 and 8. Cycles were repeated every 21 days. A two-stage flexible optimal design was applied in the phase II study, and unacceptable toxicity was the primary end point.

Results
Overall, 159 patients were enrolled: 38 in phase I and 121 in phase II studies. Cisplatin was feasible at 60 mg/m² with gemcitabine and at 40 mg/m² with vinorelbine. With the former combination, 50 of 60 (83.3%) patients were treated without unacceptable toxicity; objective responses were reported in 26 of 60 patients (43.3%; 95% CI, 30.6 to 56.8); median progression-free and overall survivals were 25.3 and 43.6 weeks, respectively. With the latter combination, 50 (82.0%) of 61 patients were treated without unacceptable toxicity; objective responses were reported in 22 of 61 patients (36.1%; 95% CI, 24.2 to 49.4); median progression-free and overall survivals were 21.1 and 33.1 weeks, respectively.

Conclusion
Both cisplatin (60 mg/m²) plus gemcitabine and cisplatin (40 mg/m²) plus vinorelbine are feasible and active in the treatment of elderly patients with advanced NSCLC. The former combination, which provides a higher dose of cisplatin, deserves comparison versus single-agent chemotherapy in this setting of patients.
## MILES 02: Results

<table>
<thead>
<tr>
<th></th>
<th>CDDP 40 mg/m² + VIN</th>
<th>CDDP 60 mg/m² + GEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Pts</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td># (%) unaccept. Toxicity cyc 1–3</td>
<td>11/61 (18.1%)</td>
<td>10/60 (16.7%)</td>
</tr>
<tr>
<td>Response rate</td>
<td>36.1% (24.2%–49.4%)</td>
<td>43.3% (30.6%–56.8%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>21.1 weeks (15.9–28.4)</td>
<td>25.3 weeks (22.6–32)</td>
</tr>
<tr>
<td>Median OAS</td>
<td>33.1 weeks (23.1–57.7)</td>
<td>43.6 weeks (35–56.3)</td>
</tr>
</tbody>
</table>
JCOG 0803/WJOG 4307L phase III trial in advanced NSCLC elderly patients

Randomization

Age >70 yrs
IIIB-IV NSCLC
PS 0–1

Weekly Docetaxel
DOC 60 mg/m²
day 1
every 3 weeks

Weekly CDDP + Docetaxel
CDDP 25 mg/m²
DOC 20 mg/m²
day 1, 8, 15
every 4 weeks

Abe T et al. J Clin Oncol 2011;29:Abstract 7509
JCOG 0803/WJOG 4307L
stopped at first planned interim analysis

<table>
<thead>
<tr>
<th></th>
<th>Taxotere</th>
<th>CDDP + Taxotere</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Pts</td>
<td>137</td>
<td>139</td>
</tr>
<tr>
<td># Toxic deaths</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Median OS</td>
<td>17.3 mos</td>
<td>13.3 mos</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.55 [0.976–2.485]</td>
<td></td>
</tr>
<tr>
<td>Probability CDDP + TXT superior to TXT at final analysis</td>
<td>0.966%</td>
<td>–</td>
</tr>
</tbody>
</table>

Abe T et al. Proc ASCO 2011
IFCT Trial: Study scheme

NSCLC
Stage III–IV
Age 70–89 years
PS 0–2
n=451

Vinorelbine
or
Gemcitabine*

Carboplatin +
Paclitaxel^
## Response rate

<table>
<thead>
<tr>
<th></th>
<th>Single Agent Arm A (n = 211)</th>
<th>Doublet Arm B (n = 210)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>23 (10.9%)</td>
<td>61 (29.05%)</td>
<td>&lt;10^{-5}</td>
</tr>
<tr>
<td>ST</td>
<td>96 (45.5%)</td>
<td>81 (38.57%)</td>
<td>0.18</td>
</tr>
<tr>
<td>DCR (PR + ST)</td>
<td>119 (56.4%)</td>
<td>142 (67.62%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PD</td>
<td>46 (21.8%)</td>
<td>15 (7.14%)</td>
<td>&lt;10^{-4}</td>
</tr>
<tr>
<td>Not reported</td>
<td>15 (7.11%)</td>
<td>20 (9.53%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Withdrawal before 1st evaluation*</td>
<td>31 (14.7%)</td>
<td>33 (15.7%)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Overall survival

- **Single** agent:
  - MST = 10.3 months (95% CI 8.3–13.3)
  - 1-year survival 45.1% (95% CI 38.2–51.8)

- **Doublet** agent:
  - MST = 6.2 months (95% CI 5.3–7.4)
  - 1-year survival 26.9% (95% CI 21–33.1)

\[ p=0.00004 \]

### Hematological toxicity

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>Arm A Single agent</th>
<th>Arm B Doublet</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem n=149</td>
<td>VNR n=61</td>
<td>All n=210</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (4.7%)</td>
<td>23 (37.7%)</td>
<td>30 (14.3%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0 (0%)</td>
<td>6 (9.84%)</td>
<td>6 (2.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (2.01%)</td>
<td>6 (9.84%)</td>
<td>9 (4.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1.34%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

# Non hematological toxicity

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>Arm A Single agent</th>
<th>Arm B Doublet</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem n=149</td>
<td>VNR n=61</td>
<td>All n=210</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (6.04%)</td>
<td>4 (6.56%)</td>
<td>13 (6.2%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (1.34%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (0.67%)</td>
<td>1 (1.64%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.67%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (2.01%)</td>
<td>1 (1.64%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Reduced general condition</td>
<td>1 (0.67%)</td>
<td>2 (3.28%)</td>
<td>3 (1.5%)</td>
</tr>
</tbody>
</table>

### Deaths

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=168)</td>
<td>(n=143)</td>
<td></td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>3 (1.83%)</td>
<td>9 (6.62%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cancer</td>
<td>149 (90.90%)</td>
<td>112 (82.40%)</td>
<td></td>
</tr>
<tr>
<td>Intercurrent disease</td>
<td>8 (4.88%)</td>
<td>14 (10.30%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2.44%)</td>
<td>1 (0.74%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

A meta-analysis including 12 randomized trials of single agent versus doublet chemotherapy has been done.

Even including the French phase III trial no statistically significant survival advantage for doublet even with platin-based chemotherapy has been observed (HR 0.90).

Comparison of the efficacy and safety of single-agent and doublet chemotherapy in advanced non-small cell lung cancer in the elderly: A meta-analysis

Gaetan Des Guetz\textsuperscript{a,*}, Bernard Uzzan\textsuperscript{b}, Patrick Nicolas\textsuperscript{b}, Dominique Valerye\textsuperscript{c}, Georges Sebbane\textsuperscript{d}, Jean-François Morere\textsuperscript{a}

Critical Reviews in Oncology/Hematology xxx (2012) xxx–xxx

With platinum salt

Lilenbaum, 2005
0.94 [0.75; 1.17]

Sederholm, 2005
0.74 [0.51; 1.08]

Kang, 2009
1.18 [0.87; 1.60]

Quoix, 2010
0.84 [0.52; 0.79]

Abe, 2011
1.18 [0.83; 1.66]

Without platinum salt

Comella (PvsGP), 2001
0.74 [0.56; 0.98]

Comella (GvsGV), 2001
0.95 [0.74; 1.21]

Griewell (GvsGV), 2003
1.06 [0.87; 1.30]

Griewell (VsGV), 2003
1.17 [0.95; 1.44]

Fresci, 2004
0.81 [0.67; 0.98]

Hainsworth, 2007
1.01 [0.89; 1.14]

Karampeazis, 2010
0.71 [0.64; 1.59]

Overall survival with Platinum salt
0.90 [0.70; 1.16]

Overall survival without Platinum salt
0.94 [0.84; 1.07]

Overall survival (random model)
0.92 [0.82; 1.03]

MILES Phase III Randomised Trial

Advanced NSCLC
Age: ≥70
PS 0–1
Primary endpoint: OS

Gemcitabine
(1200 mg/m² d 1–8/q21)

Cisplatin + Gemcitabine
(60 mg/m² d1+1000 mg/m² d1–8/21)

PI: Cesare Gridelli, “S.G. Moscati” Hospital- Avellino (Italy)
EDITORIAL COMMENT

Histology-based treatment: a new scenario in the management of advanced nonsmall cell lung cancer

Cesare Gridelli

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Tel: +39 0825 203573; fax: +39 0825 203556;
e-mail: cgridelli@libero.it

Current Opinion in Oncology 2009, 21:97–98

In clinical practice, particularly in patients with metastatic disease, frequent diagnosis is performed by fine needle aspiration biopsy (FNAB) that produces a general cytological NSCLC diagnosis. When possible, we should always try to obtain a tumor sample tissue for a subtype of histological diagnosis, even using more invasive approaches. In a future era of treatments guided by molecular biomarkers, this will be mandatory, though waiting to obtain a molecular characterization of circulating tumor cells that may provide a noninvasive strategy [12]. However, to date, we need a sure diagnosis in order to administer a well tolerated and optimal treatment to our patients.
Non-squamous NSCLC: Cis/Pem preplanned subset analysis

OS: cis/pem vs. cis/gem (phase III)

Phase III PC vs GC Trial: Study Design

1st line treatment for advanced NSCLC

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m²

Q 3 weeks x 6 cycles

Gemcitabine 1250 mg/m² d 1, 8 + Cisplatin 75 mg/m²

Primary endpoint: Overall survival (non-inferiority)
Secondary endpoints: RR, Response duration, PFS, TTP, TTF, Tox

MILES 04 Phase III Randomised Trial

SQUAMOUS

- Gemcitabine (1200 mg/m² d 1–8/q21)
- Cisplatin + Gemcitabine (60 mg/m² d1+1000 mg/m² d1–8/21)

NON SQUAMOUS

- Gemcitabine (1200 mg/m² d 1–8/q21)
- Cisplatin + Gemcitabine (60 mg/m² d1+1000 mg/m² d1–8/21)
- Pemetrexed (500 mg/m² d 1/q21)
- Cisplatin + Pemetrexed (60 mg/m² d1+500 mg/m² d1/21)

PI: Cesare Gridelli, “S.G. Moscati” Hospital- Avellino (Italy)
EPIC Trial: Elderly Patients Individualized Chemotherapy Trial

2:1 Randomization

Individualized Arm

Squamous Cell Carcinoma

Yes

ERCC1 low RRM1 high
Carboplatin

ERCC1 high RRM1 low
Gemcitabine

ERCC1 low RRM1 low
Carbo/Gem

ERCC1 high RRM1 high
Taxane

Control Arm

Treatment based on Investigators’ Preference

No

EGFR Mut +
Yes

Off Study

No

EGFR Mut +
Yes

RMM1 low

RMM1 high

Carboplatin

Pemetrexed

Carbo/Pem

ERCC1 low TS high

ERCC1 high TS low

ERCC1 low TS low

ERCC1 high TS high

RMM1 low

RMM1 high

Gemcitabine

Taxane

PIs: G. Simon, Prof. Giorgio Scagliotti University of Turin, Orbassano (Italy)
Outcomes for elderly A-NSCLC pts (28%) treated with bevacizumab + carboplatin and paclitaxel

Retrospective Analysis of ECOG 4599 Trial

Conclusion

In elderly NSCLC patients, PCB was associated with a higher degree of toxicity, but no obvious improvement in survival compared with PC. Data from this unplanned, retrospective analysis justify prospective evaluation of the therapeutic index of PCB regimen in elderly patients.

Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 Study (AVAiL)

**Conclusions:** This analysis of the randomized, phase III AVAiL trial shows that bevacizumab-based therapy improves outcomes for elderly patients with non-small cell lung cancer. Furthermore, bevacizumab-based therapy is well tolerated in elderly patients.

**Kaplan-Meier estimates for progression-free survival (PFS) (intent-to-treat population) for patients aged 65 years or older and patients younger than 65 years**

- Placebo + CG
- Bevacizumab 7.5 mg/kg + CG
- Bevacizumab 15 mg/kg + CG
Thirty-one elderly patients over 75 years affected by advanced NSCLC harboring an activating EGFR mutation received first-line gefitinib.

The treatment was well tolerated and showed similar results as compared to younger patients included in phase III randomized trials.

Response rate: 74%; PFS: 12.1 mos; OS: 33.8 mos

Conclusions

- Treatment of advanced NSCLC in the elderly is a challenging and emerging issue

- No agreement on the definition of “elderly” (65 – 70 – 75 years ?)

- “Biological” age rather than "chronological" age should guide medical decision

- Geriatric assessment welcome but to date no easy tools available and limited evidence that it impacted treatment decision making

- Very few specifically designed phase III trials

- Role of carboplatin-based chemotherapy needs to be confirmed with more feasible regimens

- Role of cisplatin-based chemotherapy needs to be investigated

- Targeted therapies welcome but consider toxicity

- Very few data on chemotherapy in octogenarians
THANK YOU!