Practical management of patients in advanced non-small cell lung cancer (NSCLC) cisplatin or carboplatin combination therapies

Marina Chiara Garassino, MD
Department of Medical Oncology 1, Fondazione IRCSS, Istituto Nazionale dei Tumori, Milano, Italy

Antonio Rossi, MD
Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy
Agenda

- Platinum compounds pharmacology
- Platinum compounds vs. BSC
- Platinum compounds vs. a single agent
- Cisplatin vs. carboplatin
- Conclusions
Platinum compounds

- Cisplatin:
  - Severe side effects (toxicity to kidneys and nervous system)
  - Resistance

- Carboplatin:
  - Widespread clinical use
  - Less toxic and fewer side effects

- Bidentate ligand is more stable; slower reaction in the body

- Oxaliplatin
  - Colon cancer

- AMD473
  - Overcome resistance
  - Sterics govern activity

Cisplatin and carboplatin pharmacology
The compound cis-PtCl2(NH3)2 was first described by M. Peyrone in 1845, and known for a long time as Peyrone's salt.

The structure was deduced by Alfred Werner in 1893.

In 1965, Barnett Rosenberg, van Camp et al. of Michigan State University discovered that electrolysis of platinum electrodes generated a soluble platinum complex which inhibited binary fission in Escherichia coli (E. coli) bacteria.

In 1969 they demonstrated the regression of sarcomas in rats.

In 1978 Cisplatin was approved for use in testicular and ovarian cancers by the U.S. Food and Drug Administration on December 19, 1978.
Cisplatin - Mechanism of action

- It is classified as an alkylating-like agent
- Following administration, one of the chloride ligands is slowly displaced by water (an aqua ligand), in a process termed aquation.
- The aqua ligand in the resulting [PtCl(H2O)(NH3)2]⁺ is itself easily displaced, allowing the platinum atom to bind to bases. Of the bases on DNA, guanine is preferred.
Cisplatin - Mechanism of action

- Subsequent to formation of \([\text{PtCl(guanine-DNA)}(\text{NH}_3)_2]+\), crosslinking can occur via displacement of the other chloride ligand, typically by another guanine.

- Cisplatin crosslinks DNA in several different ways, interfering with cell division by mitosis.

- The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when repair proves impossible.
Cisplatin

- Classic synthesis in inorganic chemistry; pioneered by Dhara in 1970

\[
K_2 \left[ \begin{array}{c} \text{Cl} & \text{Pt} & \text{Cl} \\ \text{Cl} & \text{Pt} & \text{Cl} \end{array} \right] \xrightarrow{\text{excess KI}} -4 \text{ KCl} \xrightarrow{2 \text{ NH}_3} \text{excess KI} \xrightarrow{\text{excess KCl}} \]

- Stereoselectivity

Fricker SP. Dalton Trans 2007;(43):4903-4917;
Platinum is the reactive adduct for cisplatin (coordination chemistry)

Carboplatin

- Carboplatin differs from cisplatin in that it has a bidentate dicarboxylate (CBDCA) ligand in place of the two chloride ligand, which are the leaving groups in cisplatin.

- It has also some other different mechanism of action such as its effect on MCF-7 cell lines.
Carboplatin
Are they the same?

- **Cisplatin**
  - More nephrotoxicity
  - More nausea, vomiting
  - Less Myelosuppressive effect
  - Less liver disfunction

- **Carboplatin**
  - More myelosuppressive effect
  - Less nephrotoxicity
  - Less nausea, vomiting
  - Less neurotoxicity
  - More liver toxicity
Cisplatin vs. carboplatin in solid tumours – an old and endless story

- Although the mechanism of action is similar, it is unclear whether the clinical efficacy of carboplatin and cisplatin is the same.
- For ovarian cancer their equivalent treatment efficacy has been convincingly proven.
- For germ cell and head-neck tumours, cisplatin treatment is superior when compared with carboplatin.
- No differences in efficacy between cisplatin and carboplatin in the first-line treatment of SCLC, with differences in the toxicity profile.

Platinum-based therapy vs. best supportive care
Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of events/No of patients entered</th>
<th>Supportive care plus chemotherapy</th>
<th>Supportive care</th>
<th>Observed - expected deaths</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long term alkylating agents:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxford</td>
<td>120/121</td>
<td>62/67</td>
<td>16.40</td>
<td>43.80</td>
<td></td>
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<tr>
<td>Quebec</td>
<td>20/20</td>
<td>18/18</td>
<td>-4.38</td>
<td>7.99</td>
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<tr>
<td>Subtotal</td>
<td>140/141</td>
<td>80/85</td>
<td>12.02</td>
<td>51.79</td>
<td></td>
</tr>
<tr>
<td><strong>Vinca alkaloids/etoposide:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gwent 2</td>
<td>96/111</td>
<td>67/75</td>
<td>-5.15</td>
<td>38.00</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>96/111</td>
<td>67/75</td>
<td>-5.15</td>
<td>38.00</td>
<td></td>
</tr>
<tr>
<td><strong>Cisplatin based:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLW 8351</td>
<td>84/86</td>
<td>80/81</td>
<td>-8.06</td>
<td>39.94</td>
<td></td>
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<tr>
<td>NCIC CTG</td>
<td>95/97</td>
<td>51/53</td>
<td>-11.28</td>
<td>28.24</td>
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<tr>
<td>Southampton</td>
<td>17/17</td>
<td>15/15</td>
<td>1.16</td>
<td>7.55</td>
<td></td>
</tr>
<tr>
<td>NRH</td>
<td>44/44</td>
<td>40/43</td>
<td>2.93</td>
<td>18.72</td>
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</tr>
<tr>
<td>UCLA</td>
<td>31/32</td>
<td>30/31</td>
<td>-4.83</td>
<td>14.53</td>
<td></td>
</tr>
<tr>
<td>Ancona 1</td>
<td>63/63</td>
<td>65/65</td>
<td>-5.72</td>
<td>30.95</td>
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<tr>
<td>AOI-Udine</td>
<td>52/52</td>
<td>50/50</td>
<td>-14.98</td>
<td>18.77</td>
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<tr>
<td>CEP-85</td>
<td>23/25</td>
<td>21/24</td>
<td>-10.52</td>
<td>6.61</td>
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<td>409/416</td>
<td>352/362</td>
<td>-51.31</td>
<td>165.31</td>
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<tr>
<td><strong>Total</strong></td>
<td>645/668</td>
<td>499/522</td>
<td>-44.44</td>
<td>255.09</td>
<td></td>
</tr>
</tbody>
</table>

NSCLC Collaborative Group. BMJ 1995;311:899-909
Chemotherapy in addition to supportive care improves survival in advanced NSCLC

- A systematic review and meta-analysis of individual patient data from 16 randomised controlled trials

Cisplatin significantly improves survival over Best Supportive Care (HR 0.77 CI 0.71-0.83)

It is not yet identified the best companion to be associated to cisplatin

There’s a large heterogeneity among studies

Trials are mostly small and performed with an old methodology
Platinum-based therapy vs. single-agent treatment
Addition of platinum compounds to a new agent in patients with advanced NSCLC

- A literature based meta-analysis of randomised trials

**Overall response: Two-fold higher than to single-agent**

Addition of platinum compounds to a new agent in patients with advanced NSCLC

- A literature based meta-analysis of randomised trials
- 13% improvement in OS compared with single-agent

Addition of platinum compounds to a new agent in patients with advanced NSCLC

- A literature based meta-analysis of randomised trials

**Platinum-based doublet therapy significantly increased toxicity over single-agents; no significant difference in treatment-related mortality between the two treatment modalities**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of evaluable trials</th>
<th>Combination chemotherapy</th>
<th>Single-agent therapy</th>
<th>OR (95% CI)</th>
<th>P value for Q test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of patients with toxicity (%)</td>
<td>No. of evaluable patients</td>
<td>No. of patients with toxicity (%)</td>
<td>No. of evaluable patients</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>507 (56.5)</td>
<td>897</td>
<td>281 (32.2)</td>
<td>872</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>90 (8.5)</td>
<td>1054</td>
<td>6 (0.6)</td>
<td>1041</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>7</td>
<td>62 (5.7)</td>
<td>1085</td>
<td>9 (0.8)</td>
<td>1072</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6</td>
<td>223 (21.2)</td>
<td>1054</td>
<td>60 (5.8)</td>
<td>1041</td>
</tr>
</tbody>
</table>

Platinum-based treatment vs. non-platinum based treatment
Platinum-based vs non-platinum-based chemotherapy in advanced NSCLC: A meta-analysis of the published literature

- 62% increase in the OR for platinum-based chemotherapy compared with non-platinum regimens
- The benefit was 17% in OR for response between platinum and third-generation agents

D'Addario G *et al.* J Clin Oncol 2005;23(13):2926-2936
21% increase in OR for 1-year survival in favour of platinum-based regimens

No difference OR for 1-year survival with third generation–based combination regimens

Platinum-based therapy was associated with a significant increase of anemia, neutropenia, thrombocytopenia, nephrotoxicity, nausea/vomiting. No statistically significant difference was found for neurotoxicity, febrile neutropenia, and toxic death rate.

Cisplatin-based vs. carboplatin-based treatment
Comprehensive review of cisplatin vs. carboplatin 1992-2003

- Results -
Included Studies and Patients

<table>
<thead>
<tr>
<th>Number of studies meeting criteria:</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>4</td>
</tr>
<tr>
<td>Randomized Phase II</td>
<td>1*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of studies with &gt; 100 patients per arm</th>
<th>3*</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Number of patients in these studies:</th>
<th>2306</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients treated with Cisplatin</td>
<td>1154</td>
</tr>
<tr>
<td># of patients treated with Carboplatin</td>
<td>1152</td>
</tr>
</tbody>
</table>

*100 patients per arm has previously been used as the minimally accepted number of patients per arm for consideration, also, in previous comprehensive reviews, only phase III studies have been included. For reasons of completeness, we have also included a small phase III trial and a randomized phase II study.

-Odds Ratio of 1 year survival-
Large Randomized Phase III Studies (> 100 patients/arm)

- OR of surviving 1 year if on cisplatin vs carboplatin = 1.20 (p<0.05)
- OR of surviving 2 years if on cisplatin vs carboplatin = 1.25 (p<0.1)

Increase OR in favour of cisplatin
Studies in over 2300 patients

- Comprehensive review of cisplatin vs. carboplatin 1992-2003

![Graph showing survival improvement]

Incremental survival improvement with carboplatin and cisplatin compared to best supportive care (BSC).

- Median survival:
  - BSC: 5.0 months
  - Carboplatin: 8.7 months
  - Cisplatin: 9.8 months

- Incremental benefit over BSC: 4.8 months

* All studies reported 1995-2003

** Incremental benefits:
- Carboplatin vs. supportive care: 96%
- Carboplatin vs. supportive care: 74%
- Cisplatin vs. carboplatin: 22%

Meta-analysis comparing carboplatin and cisplatin-based chemotherapy in advanced NSCLC

- 10 phase III trials comparing carboplatin-containing and cisplatin-containing regimens in advanced NSCLC from 1990 to 2003
- 3,171 patients in carboplatin regimens and 3,168 patients in cisplatin regimens
- The pooled estimate for difference in median survival is -0.36 months with 95% CI of -0.91-0.19
- The pooled estimate for 1-year survival RR is 0.99, 95% CI 0.94-1.05

Chan AM et al. J Clin Oncol 2005;23(suppl 16S):7218
Meta-analysis comparing carboplatin and cisplatin-based chemotherapy in advanced NSCLC

- The pooled estimate for overall response RR is 0.91, 95% CI 0.86-0.97
- In the subgroup analysis of carboplatin vs. cisplatin comparisons in which the non-platinum drug is the same, the pooled estimate for difference in median survival is -1.03 months with 95% CI -2.13-0.09
- There is a slight statistical superiority for cisplatin in terms of overall response
- There is a statistical trend towards a benefit in median survival in favour of cisplatin when the non-platinum drug is the same

Chan AM et al. J Clin Oncol 2005;23(suppl 16S):7218
Meta-analysis of randomised clinical trials comparing cisplatin to carboplatin in patients with advanced NSCLC

- 5% improvement in overall survival for cisplatin-based chemotherapy when compared with carboplatin-based chemotherapy not statistically significant (HR 1.050, 95% CI 0.907-1.216; p = 0.515)

Meta-analysis of randomised clinical trials comparing cisplatin to carboplatin in patients with advanced NSCLC

- Cisplatin plus a new agent yielded an 11% statistically significant superior survival as compared with that of carboplatin plus a new agent

# CISCA meta-analysis

Cisplatin vs. carboplatin in NSCLC: Trials characteristics

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Pts</th>
<th>Accrual</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>MS (months)</th>
<th>1-y S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky 1990</td>
<td>114</td>
<td>1987-1989</td>
<td>CIS 120 + Etoposide, CARBO 325 + Etoposide</td>
<td>24</td>
<td>7.1</td>
<td>33</td>
</tr>
<tr>
<td>Jelic 2001</td>
<td>112/104</td>
<td>1990-1996</td>
<td>CIS 120 + Vindesine + Mitomycin, CARBO 500 + Vindesine + Mitomycin</td>
<td>37/35</td>
<td>7.8/7.9</td>
<td>21/37</td>
</tr>
<tr>
<td>Bisset 2001</td>
<td>20/21</td>
<td>1998-1999</td>
<td>CIS 75 + Tirapazamine, CARBO AUC 6 + Tirapazamine</td>
<td>25/14</td>
<td>6.3/10.3</td>
<td>21/33</td>
</tr>
<tr>
<td>Zatloukal 2003</td>
<td>87/89</td>
<td>1999-2001</td>
<td>CIS 80 + Gemcitabine, CARBO AUC 5 + Gemcitabine</td>
<td>41/29</td>
<td>8.8/8.0</td>
<td>31/35</td>
</tr>
<tr>
<td>Mazzanti 2003</td>
<td>62/58</td>
<td>1998-2001</td>
<td>CIS 80 + Gemcitabine, CARBO AUC 5 + Gemcitabine</td>
<td>42/31</td>
<td>10.4/11.0</td>
<td>43/43</td>
</tr>
<tr>
<td>Paccagnella 2004</td>
<td>74/79</td>
<td>1994-1997</td>
<td>CIS 100 + Vinblastine + Mitomycin, CARBO 300 + Vinblastine + Mitomycin</td>
<td>42/35</td>
<td>10.0/7.2</td>
<td>33/25</td>
</tr>
</tbody>
</table>

ORR: objective response rate; MS: median survival; 1-y S: 1-year survival

Cisplatin vs. carboplatin-based chemotherapy in first-line treatment of advanced NSCLC: An individual patient data meta-analysis

Objective response was 30% for cisplatin and 24% for carboplatin with an OR for nonresponse of 1.37 (95% CI 1.16-1.61; p < 0.001)

Test for heterogeneity
- Q-test = 4.20
- p = 0.837
- I2 = 0%

Cisplatin vs. carboplatin-based chemotherapy in first-line treatment of advanced NSCLC: An individual patient data meta-analysis

- The risk of death was higher with carboplatin compared with cisplatin, although the difference was not statistically significant (HR 1.07, 95% CI 0.99-1.15; p = 0.100)

The test for heterogeneity was performed after omitting the study by Jelic et al., the only one showing a statistically significant advantage of carboplatin over cisplatin.

- **All studies**
  - Q-test = 16.8
  - p = 0.032
  - I² = 52%

- **Without Jelic study**
  - Q-test = 7.11
  - p = 0.418
  - I² = 2%

HR for mortality in patients with non-squamous NSCLC was 1.12 (95% CI 1.01-1.23), whereas in the subgroup with squamous histology, it was 0.97 (95% CI 0.85-1.10). HRs for mortality were 0.94 (95% CI 0.80-1.11) and 1.11 (95% CI 1.01-1.21) in the subgroups of patients treated with second- and third-generation regimens, respectively. Third-generation regimens were administered to 2,330 patients, 80% of the total population.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous histology</td>
<td>1.12</td>
<td>1.01-1.23</td>
<td>0.026</td>
</tr>
<tr>
<td>Squamous histology</td>
<td>0.97</td>
<td>0.85-1.10</td>
<td>0.586</td>
</tr>
<tr>
<td>II generation CT</td>
<td>0.94</td>
<td>0.80-1.11</td>
<td>0.467</td>
</tr>
<tr>
<td>III generation CT</td>
<td>1.11</td>
<td>1.01-1.21</td>
<td>0.026</td>
</tr>
</tbody>
</table>

CISCA meta-analysis
Cisplatin vs. carboplatin in NSCLC:
Grade 3-4 toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CISplatin % patients</th>
<th>CArboplatin % patients</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>33</td>
<td>32</td>
<td>0.96 (0.81-1.14)</td>
</tr>
<tr>
<td>NEU</td>
<td>54</td>
<td>53</td>
<td>0.95 (0.80-1.12)</td>
</tr>
<tr>
<td>HB</td>
<td>12</td>
<td>13</td>
<td>1.10 (0.87-1.40)</td>
</tr>
<tr>
<td>PLT</td>
<td>6</td>
<td>12</td>
<td>2.27 (1.71-3.01)*</td>
</tr>
<tr>
<td>Nausea-Vomiting</td>
<td>18</td>
<td>8</td>
<td>0.42 (0.33-0.53)*</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>12</td>
<td>11</td>
<td>0.96 (0.75-1.23)</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1.5</td>
<td>0.5</td>
<td>0.37 (0.15-0.88)*</td>
</tr>
</tbody>
</table>

*Statistically significant

Cisplatin vs. carboplatin: A renewed rivalry

Activity:
- Cisplatin-based therapy better than carboplatin-based regimens in objective response rate

Efficacy:
- Cisplatin-based therapy is slightly superior than carboplatin-based regimens in terms of survival. Cisplatin-based therapy is superior than carboplatin-based regimens in terms of survival when combined with third generation agents (80% of the overall study population) and in non-squamous tumours as suggested by subgroup analyses
Cisplatin vs. carboplatin: A renewed rivalry

Toxicity:

- The range of toxicity of the two platinum agents is different
- Carboplatin-based regimens are associated with higher incidence of grade 3-4 hematological toxicities
- Cisplatin-based therapies are associated with more non-hematological toxicities of any grade
- All eligible trials started accrual during the ’80s and ’90s, it is likely that with the introduction of granulocyte colony-stimulating factors and erythropoietins which could control neutropenia and anemia and newer and more effective antiemetic agents, the incidence of these toxicities can be further ameliorated
Cisplatin vs. carboplatin: A renewed rivalry

Clinical practice recommendation:

- The choice of the platinum compound for first-line treatment of advanced NSCLC patients in the clinical practice should take into account:
  - The expected toxicity profile
  - The patient organ function
  - The comorbidities
  - The companion
Thank You!