Cisplatin is the Superior Platinum Agent in the Initial Treatment of Unresectable NSCLC

PRO
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Objectives

- Describe the pharmacological differences between cisplatin and carboplatin in doublet and triplet initial therapy for non-small cell lung cancer (NSCLC).
- Discuss the clinical trial and meta-analysis data comparing cisplatin and carboplatin in the initial management of NSCLC.
- Focus on patient and regimen characteristics that may aid in the selection of cisplatin or carboplatin preferentially in unresectable NSCLC.
- Evaluate comparative short and long-term toxicities of the two agents.
Platinum Development

Timeline | Milestones in the development of platinum drugs for cancer therapy

1965
- Discovery of the biological properties of cisplatin in bacteria.

1968
- First patient treated with cisplatin.

1971
- First patient treated with carboplatin.

1978
- Regulatory approval of carboplatin (ovarian cancer).

1982
- Regulatory approval of cisplatin (testicular and bladder cancer).

1985
- Description of the various cisplatin-induced adducts formed on DNA.

1989
- Identification of the role of elevated glutathione in causing tumour resistance to cisplatin.

1991
- Identification of the molecular defect in nucleotide-excision repair that causes hypersensitivity of some testicular cancers to cisplatin.

1992
- First clinical study showing the promise of oxaliplatin when used in combination with 5-fluorouracil in patients with colorectal cancer.

1993
- First patient treated with JM473 (picoplatin).

1997
- First patient treated with JP216 (satraplatin).

1999
- Identification of the role of the copper transporter CTR1 in transporting cisplatin into cells.

2002
- Approval of bevacizumab in non-small-cell lung cancer used in combination with carboplatin and paclitaxel.

2006
- Initial US FDA approval of oxaliplatin (colorectal cancer).

2007
- Satraplatin being considered for approval by the US FDA for prostate cancer.

The Original Platinums - Similarities

- Complexes form strong covalent bonds with purine DNA bases (platinum adducts) between guanine residues
- Common diseases
  - NSCLC, SCLC, refractory lymphoma, breast, head/neck, endometrial, esophageal, ovarian, bladder cancers
- Resistance mechanisms
  - Mediated through nucleotide excision repair (ERCC1, e.g.), increased intracellular glutathione concentrations
- Renal clearance
The Original Platinums - Differences

**Cisplatin**
- Adduct formation
  - 0.07 mM
- Toxicities
  - Nephrotoxic
  - Severe N/V
  - More neurotoxic
- Activity
  - Metastatic germ cell tumors, cervical cancer

**Carboplatin**
- Adduct formation
  - 5 mM
  - Requires 7.5 time longer incubation time *in vivo* to induce the same DNA damage
- Toxicities
  - Myelosuppressive
  - Moderate N/V
  - Less neurotoxic
- Shorter infusion time

Cisplatin versus Carboplatin

- **Dosing**
  - BSA versus AUC
    - **Carboplatin**
      - Dosing based on correlation with the pharmacodynamic outcome of thrombocytopenia (platelet nadirs of approximately 30% of the pretreatment value)
  - Cisplatin dose adjustment recommended at GFR < 50 mL/min

- **Hypersensitivity** similar with similar exposure

Initial Treatment - Advanced NSCLC

- Histology-based treatment
  - Non-squamous (adenocarcinoma, large cell or NSCLC not otherwise known)
    - EGFR mutation positive
      - Erlotinib 150 mg PO daily
      - PS 0-4
    - EGFR mutation negative or unknown
      - Platinum-based doublet
      - PS 0-1
  - Squamous
    - Platinum-based doublet
  - Either histology - EGFR + by IHC (not mutation)
    - Cisplatin/vinorelbine/cetuximab (category 2B)
    - PS 0-2
Initial Treatment - Advanced NSCLC

- Platinum-based chemotherapy recommended for all patients eligible for treatment

- Platinum combinations have shown:
  - ORR = 25-35%
  - TTP = 4-6 months
  - Median survival = 8-10 months
  - 1 year survival = 30-40%

- No specific platinum-based chemotherapy doublet is superior

NCCN Practice Guidelines: Non-Small Cell Lung Cancer v.3.2011
Up To Date

“The less nephrotoxic analog carboplatin has been substituted for cisplatin in many chemotherapy regimens (eg, ovarian cancer, non-small cell lung cancer). The relative activity of cisplatin and carboplatin in different diseases needs to be considered in determining whether or not this is a feasible approach.”

http://www.uptodate.com/contents/cisplatin-nephrotoxicity
Cisplatin is the Superior Platinum Agent in the Initial Treatment of Unresectable NSCLC

PRO
Cisplatin and NSCLC

- Preferred agent in the curative setting
  - No adjuvant data supports using carboplatin over cisplatin
- Longer retention time = better antitumor effect
- Preferred platinum for IIIB combined chemoradiation (NCCN Practice Guidelines: Non-Small Cell Lung Cancer v.3.2011)
- Up To Date - Initial systemic chemotherapy for advanced non-small cell lung cancer
  - “Improvements in the management of chemotherapy-induced vomiting and the use of lower doses of cisplatin in newer regimens have mitigated some of the concerns about cisplatin toxicity.”
Cisplatin Isn’t Evil

- Cisplatin’s evils have been greatly exaggerated
- Nausea/vomiting is no longer an issue
  - Three drug combination means complete response (no emesis, no rescue) in 73% of patients
- Nephrotoxicity
  - Minimized when:
    - Patients selected appropriately
      - No renal disease, good PS (as is true for ALL chemotherapy in NSCLC)

Cisplatin Isn’t Evil

- **Nephrotoxicity**
  - Minimized when:
    - Prehydration given
    - 1 L NS before and after
    - The right dose is used
    - Doses of $\leq 100$ mg/m2 are effective

- **Neurotoxicity**
  - Highly unlikely when $\leq 6$ cycles of chemotherapy given

CISCA (CISplatin versus CArboplatin)
Meta-analysis Group

- Trials in first line treatment with the same comparator, only difference was platinum agent used

**Methods**
- Randomized trials identified, databases obtained. Hazard ratios (HRs), odds ratios (ORs), and their 95% confidence intervals (CIs) for mortality, objective response, and toxicity were endpoints

**Results**
- Nine trials with a total of 2968 patients

CISCA (CISplatin versus CArboplatin) Meta-analysis Group

Results

- Objective response rate cisplatin (30%) carboplatin (24%); OR = 1.37; 95% CI = 1.16 to 1.61; \( P < .001 \).
- Carboplatin had non-statistically significant increase in the mortality relative to treatment with cisplatin (HR = 1.07; 95% CI = 0.99 to 1.15; \( P = .100 \)).
- In nonsquamous tumors and those treated with third-generation chemotherapy, carboplatin-based chemotherapy was associated with a statistically significant increase in mortality (HR = 1.12; 95% CI = 1.01 to 1.23 and HR = 1.11; 95% CI = 1.01 to 1.21, respectively).
- Cisplatin-based regimens - more severe nausea and vomiting and nephrotoxicity
- Carboplatin-based chemotherapy - more severe thrombocytopenia

CISCA (CISplatin versus CArboplatin) Meta-analysis Group

- Author Conclusions
  - This meta-analysis suggests that cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy in terms of response rate and, in certain subgroups, in prolonging survival without being associated with an increase in severe toxic effects.
  - Therefore, cisplatin-based third generation regimens should remain the standard reference for the treatment of selected patients with advanced-stage NSCLC and of those with earlier-stage disease.

CISCA (CISplatin versus CArboplatin) Meta-analysis Group

- Harvey Conclusions
  - You don’t die from N/V, you die from suboptimally treated NSCLC
    - And in this trial, that was shown
  - Cisplatin better in nonsquamous!
  - Not **everyone** should get cisplatin (but don’t be a wimp!)
    - Diminished hearing
    - Baseline renal impairment

How Do You Dose Carboplatin?

- Variability in creatinine measures can lead to substantial differences in AUC-based dosing

- 68 year old, 85 kg man with NSCLC in Chapel Hill getting AUC 6 with paclitaxel.
- Cycle 1, Cr = 1.1 mg/dL, dose = 614 mg, no clinically significant heme tox.
- Dr Valgus tells him “you should drink plenty of fluids”, so he does.
- Cycle 2, Cr = 0.8 mg/dL, dose = 787 mg.
- 22% difference in dose! Same patient! Same kidneys! Same cancer!

- Cisplatin 75-100 mg/m2
“Cockcroft Gault is not validated with IDMS serum creatinine. Using it will result in higher creatinine clearance values, which leads to higher doses and, therefore, a higher potential risk of toxicity. There is a need to establish consistency in practice so that the estimated CrCl amount calculated in any major cancer center is the same, reproducible estimate when calculated at any community oncology practice office. Consistency in clinical practice needs to be established and is long overdue. Ultimately, inconsistency in clinical practice contributes to undue risk in oncology patient care.”

### Practice Variability by Heme/Onc Pharmacists


<table>
<thead>
<tr>
<th>Question</th>
<th>n</th>
<th>Response %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do you use Calvert formula for dosing carboplatin? (n = 515)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>511</td>
<td>98.3%</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>1.7%</td>
</tr>
<tr>
<td><strong>How do you determine GFR for Calvert formula? (n = 489)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measured</td>
<td>29</td>
<td>5.9%</td>
</tr>
<tr>
<td>Estimated CrCl</td>
<td>460</td>
<td>94.1%</td>
</tr>
<tr>
<td><strong>What equation do you use to estimate CrCl? Check all that apply. (n = 515)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockcroft-Gault</td>
<td>460</td>
<td>89.3%</td>
</tr>
<tr>
<td>Jeliffe</td>
<td>195</td>
<td>37.9%</td>
</tr>
<tr>
<td>MDRD</td>
<td>13</td>
<td>2.5%</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>3.5%</td>
</tr>
<tr>
<td><strong>For patients in whom actual body weight is ≥20% than ideal body weight, what body weight do you use to estimate CrCl? (n = 441)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ideal body weight</td>
<td>41</td>
<td>9.3%</td>
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<tr>
<td>Actual body weight</td>
<td>247</td>
<td>86.0%</td>
</tr>
<tr>
<td>Adjusted body weight</td>
<td>153</td>
<td>34.7%</td>
</tr>
<tr>
<td><strong>In obese patients, what body weight do you use for estimating CrCl? (n = 456)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ideal body weight</td>
<td>53</td>
<td>11.6%</td>
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<tr>
<td>Actual body weight</td>
<td>191</td>
<td>41.9%</td>
</tr>
<tr>
<td>Adjusted body weight</td>
<td>212</td>
<td>46.5%</td>
</tr>
<tr>
<td><strong>In cachectic patients, what body weight do you use for estimating CrCl? (n = 470)</strong></td>
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<td></td>
</tr>
<tr>
<td>Ideal body weight</td>
<td>42</td>
<td>8.9%</td>
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<tr>
<td>Actual body weight</td>
<td>416</td>
<td>88.5%</td>
</tr>
<tr>
<td>Adjusted body weight</td>
<td>12</td>
<td>2.6%</td>
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</table>
### Practice Variability by Heme/Onc Pharmacists

**Do you use the laboratory reported value for serum creatinine? (n = 513)**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>497</td>
<td>16</td>
</tr>
</tbody>
</table>

**Do you used an adjusted/assigned value for serum creatinine when below (less than) your laboratory normal limit? (n = 512)**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>284</td>
<td>228</td>
</tr>
</tbody>
</table>

**What adjusted/assigned value do you use? (n = 225)**

<table>
<thead>
<tr>
<th>Value (mg/dL)</th>
<th>Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>60</td>
</tr>
<tr>
<td>0.8</td>
<td>101</td>
</tr>
<tr>
<td>0.9</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>55</td>
</tr>
</tbody>
</table>

**Do you convert IDMS serum creatinine to non-IDMS value prior to calculating creatinine clearance? (n = 495)**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>91</td>
<td>404</td>
</tr>
</tbody>
</table>

**Do you have an upper limit (cap) for CrCL when dosing carboplatin?**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>243</td>
<td>267</td>
</tr>
</tbody>
</table>

**If so, what is the limit?**

| Mean (mL/min) | 133 ± 15 (CV 11.3%) |
| Range (mL/min)| 100–166            |

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The Days of Carboplatin Based Therapy for Everyone with NSCLC Are Numbered

- Fewer new trials
  - Clinicaltrials.gov - search for cisplatin or carboplatin and non-small cell lung cancer
    - Cisplatin = 132 trials
    - Carboplatin = 130 trials

- Makes perfect sense - carboplatin + paclitaxel + _______ phase III trials have been negative
  - Sorafenib, figitumumab, vandetinib

- Cisplatin + pemetrexed = FDA approval!

- Carboplatin + .........
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CON
Direct Comparison of Platinum Agents

- SWOG 9509 designed to compare the investigational regimen of carboplatin/paclitaxel vs standard reference regimen of cisplatin/vinorelbine
- Primary objective was overall survival
- Recruited 440 patients at 7 different centers throughout the United States
- Conclusion of study: Carbo/Paclitaxel is equally as efficacious as Cis/Vinorelbine and better tolerated

## Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Group</th>
<th>Chemotherapy Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cisplatin 100mg/m² every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine 25mg/m² every week</td>
</tr>
<tr>
<td>B</td>
<td>Carboplatin AUC 6 every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel 225mg/m² every 3 weeks</td>
</tr>
</tbody>
</table>

Overall Survival

## Regimen Toxicity Profile

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cis/Vin</th>
<th>Carbo/Pac</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>76%</td>
<td>57%</td>
<td>(.008)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4%</td>
<td>10%</td>
<td>(\text{NS})</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>7%</td>
<td>(.001)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>4%</td>
<td>(.007)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>3%</td>
<td>13%</td>
<td>(&lt;.001)</td>
</tr>
</tbody>
</table>

Study Summary

- Cisplatin/Vinorelbine and Carboplatin/Paclitaxel produced equivalent response rates.
- Cisplatin/Vinorelbine and Carboplatin/Paclitaxel produced equivalent survival.
- Carboplatin/Paclitaxel produced fewer life-threatening toxicities, was more convenient, and better tolerated.
Direct Comparison of Platinum Agents

- ECOG randomized trial evaluating four chemotherapy regimens for the treatment of advanced non-small cell lung cancer
- Primary objective was overall survival
- Recruited over 1200 patients at 7 different centers throughout the United States
- Conclusion of Study: None of the chemotherapy regimens offered a significant advantage over the others

## Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Group</th>
<th>Chemotherapy Regimen</th>
</tr>
</thead>
</table>
| A     | Paclitaxel 135mg/m² on Day 1  
Cisplatin 75mg/m² on Day 2 |
| B     | Gemcitabine 1000mg/m² on Days 1, 8, 15  
Cisplatin 100mg/m² on Day 1 |
| C     | Docetaxel 75mg/m² on Day 1  
Cisplatin 75mg/m² on day 1 |
| D     | Paclitaxel 225mg/m² on Day 1  
Carboplatin AUC 6 on Day 1 |

Time To Progression

Overall Survival

### Regimen Toxicity Profile

<table>
<thead>
<tr>
<th></th>
<th>Cis+Pac (N=300)</th>
<th>Cis+Gem (N=293)</th>
<th>Cis+Doc (N=297)</th>
<th>Carbo+Pac (N=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC (Grade 4)</td>
<td>57%</td>
<td>39%</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>Platelet (Grade 4)</td>
<td>2%</td>
<td>28%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>14%</td>
<td>3%</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Renal Toxicity (Grades 3-5)</td>
<td>3%</td>
<td>9%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting (Grade 3-4)</td>
<td>24%</td>
<td>35%</td>
<td>21%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Study Summary

- Response rate did not differ between any regimens studied
- Overall survival did not differ between any regimens studied
- Carboplatin/paclitaxel had significantly less febrile neutropenia and grade 3-4 CINV than the cisplatin/paclitaxel regimen
- Cisplatin is NOT superior to carboplatin-based regimen in this clinical trial
Cisplatin vs Carboplatin Meta-analysis

“Carboplatin treatment was associated with a non–statistically significant increase in the hazard of mortality relative to treatment with cisplatin (HR = 1.07; 95% CI = 0.99 to 1.15; $P = .100$).”

Current NSCLC Guidelines

- European Society for Medical Oncology 2010 Consensus Conference
  - “Platinum-based chemotherapy is preferred to non-platinum-based chemotherapy in eligible patients with metastatic NSCLC”
  - “There is no standard platinum-based doublet for metastatic NSCLC”

Current NSCLC Guidelines

- ASCO Clinical Practice Guideline for Metastatic NSCLC 2009
  - “In patients with performance status of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over nonplatinum combinations”
  - “The choice of either cisplatin or carboplatin is acceptable.”

Current NSCLC Guidelines

- NCCN NSCLC Guidelines v3.2011 (Advanced Disease)
  - No specific platinum-based cytotoxic combination is clearly superior
  - Cisplatin and carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, pemetrexed
Cisplatin is the Superior Platinum Agent in the Initial Treatment of Unresectable NSCLC

PRO-Rebuttal
Comparison?

- How is comparing differing partner agents a direct comparison?
ESMO Guidelines

European Society for Medical Oncology 2010 Consensus Conference

Furthermore, once again, patients treated with third-generation compounds in conjunction with cisplatin had a longer survival as compared with those treated with carboplatin plus the same agent.”

ASCO Guidelines

ASCO Clinical Practice Guideline for Metastatic NSCLC 2009

Recommendation A5

The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but more likely to cause thrombocytopenia.

A recent meta-analysis reported that the objective response rate is higher with cisplatin therapy when compared with carboplatin therapy (30% versus 24%). For patients with advanced, incurable NSCLC, many clinicians prefer to give carboplatin-based regimens because they are better tolerated.”
Carboplatin Dosing Matters

- We may not be curing, but we have no idea if we’re under treating
- Stage IV NSCLC today is where metastatic breast cancer, multiple myeloma, follicular lymphoma and renal cell cancer have been
  - None cured with conventional treatment, but incremental gains are important
Cisplatin is the Superior Platinum Agent in the Initial Treatment of Unresectable NSCLC

CON-Rebuttal