Transition Metal-Based Anti-cancer Agents: From Cytotoxic to Targeted Chemotherapy

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09.03.2008
Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotherapy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Chemotherapy: Cytotoxic vs Targeted

- **Cytotoxic Therapy - “Cluster Bomb”**
  - Targets *general* features of cells (DNA).
  - Associated with side effects.

- **Targeted Therapy - “Smart Bomb”**
  - Targets *specific* features of cancer cells.
  - Less side effects.

US National Cancer Institute: www.cancer.org
Outline

- Platinum-based Cytotoxic Chemotharepy
  - Drugs Approved by FDA
  - Drugs in Pending Approval / Clinical Trial
  - Drugs in Development

- Platinum-based Targeted Chemotharepy

- Ruthenium-based Targeted Chemotherapy

- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Outline

■ Platinum-based Cytotoxic Chemotherapy
  • Drugs Approved by FDA
    • Cisplatin
    • Carboplatin
    • Oxaliplatin
  • Drugs in Pending Approval / Clinical Trial
  • Drugs in Development

■ Platinum-based Targeted Chemotharepy
■ Ruthenium-based Targeted Targeted Chemotherapy
■ The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Cisplatin: A Chance Discovery to a Drug

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1845</td>
<td>Peyrone’s chloride</td>
</tr>
<tr>
<td>1893</td>
<td>Structure deduced by Werner</td>
</tr>
<tr>
<td>1968</td>
<td>Anti-cancer activity observed by Rosenberg in MSU</td>
</tr>
<tr>
<td>1971</td>
<td>The first patient treated</td>
</tr>
<tr>
<td>1978</td>
<td>Approved by FDA</td>
</tr>
<tr>
<td>2008</td>
<td>Still in use</td>
</tr>
</tbody>
</table>

Timeline for Cisplatin
Cisplatin

- Brand Name: Platinol-AQ

- Each mL contains
  - Cisplatin 1 mg
  - Sodium Chloride 9 mg
  - Water for Injection

- Cisplatin could be used to treat:
  - Metastatic Testicular Tumors
  - Metastatic Ovarian Tumors
  - Advanced Bladder Cancer

- 50 mg/50 mL $18.50

- Marketed by Bristol-Myers Squibb

www.bms.com/products/data/index.html
www.bedfordlabs.com/products/ViewProductDetails?productID=47&item=3
US National Cancer Institute: www.cancer.org
Mechanism of Action of Cisplatin

Cisplatin hydrolysis regulated by chloride concentration:

[Cl-Blood] = 100 mM  
[Cl-Cell] = 3 mM

Crystal Structure of Cisplatin & DNA Intrastand Adduct

Adenine
Thymine
Guanine
Cytosine

Carboplatin: Overcome Toxicity

- Approved by FDA in 2004
- Brand Name: Paraplatin
- Each mL Contains
  - Carboplatin 10 mg
  - Water for Injection.
- Carboplatin could be used to treat:
  - Ovarian cancer that recurred after earlier chemotherapy
- 450 mg/45 mL $90.00
- Marketed by Bristol-Myers Squibb
Oxaliplatin

- Approved by FDA in 2004

- Brand Name: Eloxatin

- Each mL Contains
  - Oxaliplatin 5 mg
  - Water for Injection.

- Eloxatin could be used for:
  - Initial therapy of advanced colorectal cancer
  - Adjuvant therapy for stage III colorectal cancer

- 50 mg/10 mL $510

- Marketed by Sanofi-Aventis

www.eloxatin.com
Mechanism of Action of Carboplatin and Oxaliplatin

Outline

- Platinum-based Cytotoxic Chemotherapy
  - Drugs Approved by FDA
  - Drugs in Pending Approval / Clinical Trial
    - *Satraplatin*
    - *Picoplatin*
  - Drugs in Development

- Platinum-based Targeted Chemotherapy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Satraplatin: The First Oral Platinum Drug

- Under consideration for approval by FDA
- Brand Name: Orplatna
- Satraplatin could be used for:
  - Non-small cell lung cancer
  - Hormone refractory prostate cancer
- Developed/marketed by Spectrum Pharm.

Mechanism of Action

www.spectrumpharm.com/satraplatin.html
**Picoplatin: Overcoming Drug Resistance**

- Phase III trial about to begin
- Picoplatin could be used to treat:
  - Small-cell lung cancer
- Developed/marketed by PONIARD

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Cisplatin: Associative Mechanism → Fast → Drug Resistance

Picoplatin: Dissociative Mechanism → Slow → Less Drug Resistance

Outline

- Platinum-based Cytotoxic Chemotherapy
  - Drugs Approved by FDA
  - Drugs in Pending Approval / Clinical Trial
  - Drugs in Development
    - Rational Design of Ethacraplatin
- Platinum-based Targeted Chemotherapy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Design of Pt(IV) Active Complex

- Modifying the Axial Ligand
  - Tuning the activity of Pt (IV) Complexes
  - Molecular targeting

- Kinetically Inert
  - Reducing side reactions

Ethacraplatin: Two Birds with One Stone

Preparation of Ethacraplatin

H₂N⁺Pt⁺Cl₂

H₂O₂

H₂O, 50 °C

1 h

H₂N⁺Pt⁺Cl₂

OH

H₂N⁺Pt⁺Cl₂

acetone, 70 °C, 20 min

# Cisplatin vs Ethacraplatin

<table>
<thead>
<tr>
<th></th>
<th>IC\textsubscript{50} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF7</td>
</tr>
<tr>
<td>24 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Ethacraplatin</td>
<td>31.85</td>
</tr>
</tbody>
</table>

MCF7: Breast tumor cell line  
T47D: Breast tumor cell line  
HT29: Colon cancer cell line  
A549: Lung adenocarcinoma epithelial cell line

Family of Cytotoxic Platinum Drugs

- Cisplatin
- Carboplatin
- Oxaliplatin
- Satraplatin
- Picoplatin
- Ethacraplatin

DNA
Side Effects of Cytotoxic Platinum Drugs

- Nausea/vomiting
- Diarrhea
- Cystitis
- Sterility
- Myalgia
- Neuropathy
- Alopecia
- Pulmonary fibrosis
- Cardiotoxicity
- Local reaction
- Renal failure
- Myelosuppression
- Phlebitis
Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotherapy
  - Soluble Single-Walled Carbon Nanotubes as Delivery Systems
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Soluble Single-Walled Nanotubes (SWNT) as Longboat Delivery Systems

Intracellular Reduction

Tethered with Fluorescence

Cytotoxicity in Ntera-2-cell

SWNT-Pt (IV) vs Parent Pt (IV)

IC$_{50}$ = 0.02 µM

(Cisplatin: IC$_{50}$ = 0.05 µM)

Mechanism of Action of SWNT-Pt (IV)

- SWNT-Pt (IV) has EPR effect.

- *Enhanced Permeability and Retention (EPR) effect:* Macromolecular drugs accumulate in tumor tissues much more than they do in normal tissues.

Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotherepy
- Ruthenium-based Targeted Chemotherapy
  - Ruthenium Drugs in Clinical Trial
    - KP1019
  - Ruthenium Drugs in Development
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
KP1019

- Phase II clinical trial about to begin.
- KP1019 could be used to treat autochthonous colorectal tumors.

Mechanism of Action of KP1019

Infusion → KP1019 → Blood → Ru III – Transferrin Adducts → Tumor

- Release of Ru III
- Reduction to Ru II
- Adducts with DNA

Activity of KP1019 in vivo

Activity of drugs in autochthonous colorectal tumors of the rat

Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotherapy
- Ruthenium-based Targeted Chemotherapy
  - Ruthenium Drugs in Clinical Trial
  - Ruthenium Drugs in Development
    - Design of Organo-Ruthenium Protein Kinase Inhibitor
    - Development of a Trojan Horse for Cancer Cells
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery
Design of Organo-Ruthenium Protein Kinase Inhibitor (Pim-1)

Pim-1 Kinase Inhibitor:

- Globular shape
- Lactam moiety
- Maintain the active moiety and globular shape
- Reduce the synthetic effort
- Stable metal complex

Synthesis of Ruthenium Complex

$$\textit{R} = \textit{OH}$$

Synthesis of Ruthenium Complex

Synthesis of Ruthenium Complex

\[
\text{phenyl-NH}_2 \cdot \text{HCl} + \text{pyridine-2-carboxylic acid} \xrightarrow{\text{iBuOH, reflux}} \text{Sulfonamide, 100%}
\]

\[
\xrightarrow{\text{TMS polyphosphate, 115 °C}} \text{Intermediate, 65%}
\]

\[
\xrightarrow{\text{LiHMDS, THF, -15 °C}} \text{TBS protection, 64%}
\]

Synthesis of Ruthenium Complex

R = H

Crystal Structure of Pim-1 with (S)-Ruthenium Complex

Ruthenium Complex vs Staurosporine

Ruthenium Complex vs Staurosporine

Differences Between Two “Isomers”

IC$_{50}$ = 25 nM

IC$_{50}$ = 220 pM
Differences Between Two “Isomers”

Development of a Trojan Horse for Cancer Cells

Development of a Trojan Horse for Cancer Cells

Activity of Trojan Horse Complex

<table>
<thead>
<tr>
<th>Complex</th>
<th>IC$_{50}$ [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Pt(acac)$_2$]</td>
<td>Inactive</td>
</tr>
<tr>
<td>Trojan Horse</td>
<td>23</td>
</tr>
<tr>
<td>Trojan Horse + [Pt(acac)$_2$]</td>
<td>12</td>
</tr>
</tbody>
</table>

Cytotoxicity in Human A2780 Ovarian Cancer Cells

- “Cisplatin rapidly leaches from the trojan horse.”
- Mechanism of Action?

Enhanced Permeability and Retention Effect

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The Challenges

- Prodrug – Only fully activated in a living system.

- Identification of new biological target beyond DNA.

- Prejudice against metal-based drugs based on their perceived toxicity.

## Periodic Table of the Elements

**Transition Metals**
- Lithium
- Aluminum
- Titanium
- Vanadium
- Chromium
- Manganese
- Iron
- Cobalt
- Nickel
- Copper
- Zinc
- Gallium
- Germanium
- Arsenic
- Selenium
- Bromine
- Krypton

**Nonmetals**
- Hydrogen
- Helium
- Nitrogen
- Oxygen
- Fluorine
- Neon

**Other Metals**
- Sodium
- Magnesium

**Total Elements:** 114
**Non-metal Elements:** 22
**Transition Metals:** 40
Acknowledgement

Dr. Wulff

Dr. Borhan

Aman, Li, Anil, Munmum, Nilanjana, Yong, Dmytro, Wynter, Maria, Ding, Alex

Allison, Chrysoula, Mercy