Chemotherapy Toxicities: Urothelial Carcinoma

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Disclosures

• Speaker Bureau: Pfizer, J&J, Sanofi, Novartis, MSD

• Advisory Board/Consultant: GSK, Novartis, Bayer, J&J, Mundipharma, Astellas, MSD, BMS, Eisai

• Research support: Sanofi, J&J, Astellas
Objectives

- Describe the chemo drugs used (based on guidelines)
- Describe the common adverse effects of each anticancer agent
- Discuss some strategies to prevent and/or manage toxicities of anticancer agents
### PRINCIPLES OF SYSTEMIC THERAPY

**First line systemic therapy for locally advanced or metastatic disease (Stage IV)**

<table>
<thead>
<tr>
<th>Cisplatin eligible</th>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine and cisplatin⁴ (category 1)</td>
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<tr>
<td></td>
<td>DDMVAC with growth factor support (category 1)²,⁸</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cisplatin ineligible</th>
<th>Preferred regimens</th>
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<tbody>
<tr>
<td></td>
<td>Gemcitabine and carboplatin¹¹</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab¹²</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab¹³</td>
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</table>

**Other recommended regimens**

|                     | Gemcitabine¹⁴ |
|                     | Gemcitabine and paclitaxel¹⁵ |

**Useful under certain circumstances**

|                     | Ifosfamide, doxorubicin, and gemcitabine¹⁶ (for patients with good kidney function and good PS) |

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹⁷
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
- Participation in clinical trials of new or more tolerable therapy is recommended.
<table>
<thead>
<tr>
<th>Categories of agents</th>
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<tbody>
<tr>
<td>■ Alkylating Agents</td>
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<tr>
<td>■ Antimicrotubules</td>
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<tr>
<td>- Vinca Alkaloids</td>
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<tr>
<td>- Taxanes</td>
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<td>■ Antimetabolites</td>
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<tr>
<td>- Folate Antagonists</td>
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<td>- Purine Analogues</td>
</tr>
<tr>
<td>- Pyrimidine Analogues</td>
</tr>
<tr>
<td>■ Enzyme inhibitors</td>
</tr>
<tr>
<td>- Topoisomerase II inhibitors</td>
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</tbody>
</table>
Alkylators – Class Effect

- **Dose limiting toxicity = myelosuppression**
  - Usually, neutropenia and thrombocytopenia

- **Other toxicities common to most agents**
  - Nausea and vomiting
  - Alopecia
  - Infertility
  - Secondary leukemias
Platinum Analogues

- Alkylating-like agents which form a reactive electrophile that covalently binds to DNA

- Agents available:
  - Cisplatin
  - Carboplatin
Cisplatin-Induced Nausea and Vomiting

Cisplatin-Induced Nephrotoxicity

- Deterioration of renal function and electrolyte wasting

- Preventive Strategies:
  - Avoid in patient with renal dysfunction
  - Hydration w/ at least 1-2 L 0.9% NaCl IV pre- and concurrent with cisplatin, with potassium & magnesium supplementation
  - Maintain urine output >100 ml/h
  - Provide mannitol and/or furosemide
  - Prolong infusion time (e.g. 24 hour infusion)
  - Amifostine
Other Cisplatin-Induced Toxicities

• **Ototoxicity** (may be irreversible)
  - Related to high peak doses
  - Unable to hear high pitch sounds

• **Peripheral neuropathy** (may be reversible) - symptoms present in 50% of patients after 300-500 mg/m² cumulative dose
  - Limit cumulative doses
  - Decrease dose or discontinue treatment
  - Substitute with carboplatin (but may compromise the treatment of some cancers)
  - Medications to reduce neuropathic pain

• Irritant to veins
Carboplatin

Unique dosing method – based on Calvert equation; some protocols may still use the BSA to calculate dose

- Dose = AUC X (CrCl + 25)
  - Use AUC = 2 for weekly dosing and AUC=5 or 6 for every 3 weeks

- What is the carboplatin dose if an oncologist wants to give the drug every 3 weeks, in a patient with CrCl = 75 ml/min?

Dose limiting myelosuppression (especially thrombocytopenia)

Comparing to cisplatin, much lower incidence of nephrotoxicity, ototoxicity and delayed nausea and vomiting

Hypersensitivity – can occur after 6-7 doses of carboplatin
Categories of agents

- Alkylating Agents
- Antimicrotubules
  - Vinca Alkaloids
  - Taxanes
- Antimetabolites
  - Folate Antagonists
  - Purine Analogues
  - Pyrimidine Analogues
Antimicrotubules (Vinca Alkaloids)

- Vinflunine (Javlor)
- Vinblastine (part of MVAC)

**MOA:** Binds to tubulin, a protein that compromised of alpha and beta subunits, inhibit its polymerization. (Polymerization of tubulin is responsible for the formation of the mitotic spindle during the metaphase period of mitosis)

Vinca Rosea
Vinca Alkaloids

- MUST adjust doses when patient experiences hepatic dysfunction!
- Many drug interactions (substrate for CYP3A4)
- Agents are potent vesicants, apply warm pack and administer hyaluronidase 1ml as an antidote
- Intrathecal administration of these agents is **FATAL**

<table>
<thead>
<tr>
<th>Year</th>
<th>USA/Canada</th>
<th>Europe</th>
<th>Australia</th>
<th>Asia</th>
<th>Total</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to 1985</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>1986–1990</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>4 (66%)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>2001–2005</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>8 (100%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>8</strong></td>
<td><strong>3</strong></td>
<td><strong>5</strong></td>
<td><strong>32</strong></td>
<td><strong>27 (84%)</strong></td>
</tr>
</tbody>
</table>
### Vinflunine Toxicities

#### Table 4. Most Common Treatment-Related Adverse Events and Hematologic Abnormalities

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>VFL + BSC*</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall Incidence</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>No. of Patients %</td>
<td>No. of Patients %</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>124</td>
<td>50.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>97</td>
<td>39.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>72</td>
<td>29.0</td>
</tr>
<tr>
<td>Stomatitis/mucositis</td>
<td>71</td>
<td>28.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>39</td>
<td>15.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>118</td>
<td>47.6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>40</td>
<td>16.7</td>
</tr>
<tr>
<td>Neuropathy sensory</td>
<td>30</td>
<td>12.1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>72</td>
<td>29.0</td>
</tr>
<tr>
<td>Infusion/injection site reaction</td>
<td>68</td>
<td>27.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>229</td>
<td>93.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>190</td>
<td>77.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>126</td>
<td>51.2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15</td>
<td>6.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** VFL, vinflunine; BSC, best supportive care.
*One pancytopenia drug-related death.*
Vinblastine

- Specific to Vinblastine
  - Dose limiting neutropenia and thrombocytopenia

- Neurologic toxicity and constipation can also occur but much less than vinflunine
**Antimicrotubules (Taxanes)**

- Mechanism of action: similar to vincas; except the taxanes bind preferentially to the microtubules shifting the microtubules towards polymerization – the taxanes then stabilize against depolymerization

- Commonly used for many cancer types

- Hepatic dose adjustment required

*Bark and Needle of Yew Tree*
Premedications Required for Taxanes

- **Paclitaxel (Taxol®, Anzatax®):**
  - **PREMEDICATIONS**
    - Hypersensitivity
    - H1-blocker, H2-blocker, Corticosteroids
    - Albumin stabilised nanoparticle version (Abraxane®) – no premed!

- **Docetaxel (Taxotere®):**
  - **PREMEDICATIONS**
    - Edema
    - Dexamethasone starting on the day before chemo
Comparison of toxicity profiles among different taxanes

<table>
<thead>
<tr>
<th>Effect</th>
<th>Paclitaxel Every 3 Wk</th>
<th>Weekly Paclitaxel</th>
<th>Docetaxel Every 3 Wk</th>
<th>Weekly Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia†</td>
<td>4</td>
<td>2</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia†</td>
<td>&lt;1</td>
<td>1</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>&lt;1</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Grade 3 or 4 neuropathy</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Grade 2, 3, or 4 neuropathy</td>
<td>20</td>
<td>27</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Categories of agents

- Alkylating Agents
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The anti-metabolites are drugs that are structurally related to naturally occurring compounds found in the body (amino acids, DNA, RNA).

These agents exert their damage on DNA in one of two mechanisms:

- Compete for binding sites on enzymes
  - Antifolate Agents (Methotrexate)

- Incorporate directly into DNA or RNA
  - Analogues (Purine and Pyrimidine)
Methotrexate

- Toxicities:
  - Dose limiting myelosuppression, nephrotoxicity, mucositis, diarrhea, hepatitis, pulmonary pneumonitis, central nervous system toxicities

- Avoid administration of drugs that interfere with methotrexate excretion
  - NSAIDs
  - Penicillins
  - Ascorbic acid (Vitamin C)
  - Probenecid, Sulfonamides
  - Salicylates
  - Omeprazole

- Monitoring
  - Daily renal function until methotrexate levels are below desired range
  - Alkalization of urine
  - Daily methotrexate levels, at 24 hour intervals
  - Fluid balance
Antimetabolites (Pyrimidine Analogue)

- Gemcitabine (Gemzar®)
- MOA: Pyrimidine analogue, inhibits synthesis of DNA/RNA
Gemzaar SE

- Flu-like symptoms (muscle pain, fever, headache, chills, fatigue)
- Fever (within 6-12 hours of first dose)
- Fatigue.
- Nausea (mild)
- Vomiting.
- Poor appetite.
- Skin rash.
- Low blood counts.
Anthracyclines

- Doxorubicin (Adriamycin®)
- Liposomal Doxorubicin (Caelyx®)

Three Mechanism of actions:

1. Induce formation of covalent topoisomerase II DNA complexes – this inhibition prevents the relegation of DNA during DNA replication causing DNA strand breaks

2. Intercalations between base pairs in the DNA are formed causing DNA breaks

3. Metabolized in the liver to form oxygen free radicals – can add to cytotoxicity
Anthracyclines: Issues

- Dose Adjustment in Hepatic impairment

- Toxicities
  - Dose limiting myelosuppression – primarily neutropenia
  - Alopecia
  - Acute nausea and vomiting
  - Vesicant – related to extravasation
  - Can cause red discoloration of urine, require patient education
Extravasation of doxorubicin

- Management:
  - Cold Compress
  - Topical DMSO
  - Dexrazoxane
- Surgical consult if necessary

Initial presentation

After surgical debridement
Anthracycline-Induced Cardiotoxicity

- **Pathophysiology**
  - Acute (24 hours): Arrhythmias, Pericarditis
  - Subacute (weeks to months): Tachycardia
  - Late (> 5 years): Cardiomyopathy

- **Risk factors:**
  1. Cumulative doses
  2. Administration schedule (high peaks)
  3. Age
  4. Mediastinal radiation
  5. Known cardiac disease
Summary

- Chemotherapy is still the mainstay of treatment of metastatic urothelial cancer.

- The SE profile of the common chemo drugs used in mUC is well known and can be managed.

- Important to recognise these SE and to address them early.