Uridine Triacetate is a Lifesaving Treatment for 5-Fluorouracil Toxicity

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Background
5-fluorouracil (5-FU) is widely used to treat solid tumors and is typically administered as a 1 to 4 day IV infusion or in the form of oral capcitabine, at or near the maximum tolerated doses. Life-threatening or lethal toxicity can be caused by innate exaggerated susceptibility to 5-FU toxicity, or by errors such as pump misprogramming or dosage miscalculations.

Uridine Triacetate (Vistaqor®) was approved by FDA in December 2015. It is an orally bioavailable produg of uridine, a pyrimidine analog indicated for the emergency treatment of adult and pediatric patients.

Following an overdose of 5-FU or capcitabine regardless of the presence of symptoms, or
- Who exhibit early-onset severe or life-threatening toxicity affecting the cardiac and central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., GI toxicity and/or neutropenia) within 96 hours following the end of the 5-FU or capcitabine administration (proctologic animal data demonstrated better survival with earlier administration of uridine triacetate).

Early-Onset, Severe 5-Fluorouracil Toxicity
Potentially catastrophic toxicities
- Severe GI: mucositis, GI ulceration, diarrhea
- Cardiac: MI, arrhythmia, LV dysfunction, cardiac arrest
- Neuro: altered mental status, cerebellar ataxia, coma
- Hematologic: neutropenia, leukopenia, thrombocytopenia

Increased susceptibility to 5-FU/capcitabine toxicity is due to a number of factors
- Impaired clearance caused by various mechanisms
- Dihydropyrimidine dehydrogenase deficiency (DPD, partial or complete) in 3-5% of patients treated with 5-FU
- Elevated OPRT (the principal enzyme that directly converts 5-FU to toxic intracellular 5-fluorouracil nucleotides)

An oral prodrg of uridine
- Uridine is a specific pharmacologic antidote for 5-FU poisoning. Poor oral bioavailability of uridine (~7%) and complications during its infusion preclude use of uridine itself as a viable antidote.
- Uridine triacetate is efficiently absorbed (more lipophilic than uridine, not a substrate for uridine phosphorylase, does not require transport), and is rapidly converted to circulating uridine by deacetylation.
- Uridine triacetate improves uridine delivery to 4 to 7-fold.
- Improves survival after lethal 5-FU overdose or DPD inhibition in mice, and earlier treatment improves outcome 1
- Clinical and nonclinical data support earlier treatment with uridine triacetate is more effective for reducing toxicity.

Historical Case (Supportive Care Only) Comparators
- It is well established that 5-FU overdose and severe toxicity can lead to death
- Data for overdose patients (n=47) were obtained from publicly-available sources (FDA, ISMP, available literature, medicolegal cases)

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Mean age, yrs (SD)</th>
<th>57.7 (16.0)</th>
<th>57.0 (12.8)</th>
<th>57.6 (15.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>46 (41.4)</td>
<td>13 (34.2)</td>
<td>40 (57.5)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6 (54.)</td>
<td>6 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>10 (83.3)</td>
<td>10 (26.3)</td>
<td>12 (16.7)</td>
</tr>
<tr>
<td>All others</td>
<td>5 (41.7)</td>
<td>5 (13.1)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>N/A (overdose)</td>
<td>5 (41.7)</td>
<td>5 (13.1)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Presenting (Week 1 toxicities)**</td>
<td>50 (40.2)</td>
<td>18 (75.0)</td>
<td>58 (84.4)</td>
</tr>
<tr>
<td>Skin/subcutaneous</td>
<td>7 (7.1)</td>
<td>4 (16.7)</td>
<td>11 (16.7)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>21 (11.7)</td>
<td>6 (23.1)</td>
<td>25 (35.7)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4 (3.3)</td>
<td>1 (4.1)</td>
<td>5 (7.1)</td>
</tr>
</tbody>
</table>

*Breast, gastric, head and neck. ** Most adverse events demonstrated signs and symptoms of toxicity at the time of administration of uridine triacetate.

Recovery Characteristics
- Patients experienced infrequent, mild to moderate adverse events attributed to uridine triacetate (vomiting 10%, nausea 5%, diarrhea 3%)
- One patient receiving uridine triacetate experienced Grade 3 nausea and vomiting.
- Of the 135 patients treated with uridine triacetate, there were 5 deaths due to 5-FU toxicity (4%). Of these 2 were treated >96 hours following the end of 5-FU administration.
- Toxicities showed a general decrease over the 4 weeks of observation.
- The overall incidence of Grade 3 or 4 mucositis was low in patients who received uridine triacetate.
- No overdose patient who received uridine triacetate developed Grade 4 mucositis at any point in the 30 day window.
- Of the 106 patients with a cancer diagnosis, 40 resumed chemotherapy within 30 days, indicative of accelerated recovery from toxicity.

Conclusions
- For patients with rapid-onset severe 5-FU toxicity or 5-FU overdose, uridine triacetate was a safe and effective life-saving treatment.
- Uridine triacetate increased the chances of faster recovery and, in some cases, earlier return to chemotherapy

Uridine Triacetate

- Improved almost all patients treated with uridine triacetate survived at 30 days or returned to chemotherapy within 30 days.
- The majority (84.9%) of supportive care only (historical) cases did not survive.

Overnight Survival

- The primary causes of 5-FU overdose were pure 5-FU malfunctions (16%), programming errors (15%), and incorrect dosing (5%).
- There were 5 cases of accidental or suicidal capcitabine ingestion (including 3 pediatric patients).
- Signs and symptoms of 5-FU toxicity were present in both early-onset and overdose patients.

References
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