Folinic Acid Rescue after Methotrexate Graft Versus Host Disease Prophylaxis to Reduce Mucositis and Improve the Probability of Day +11 Methotrexate Administration – Role of the Hematopoietic Cell Transplant Pharmacist in Development of Program Guidelines

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Disclosures

No relevant financial relationships

Learning Objectives

• Describe the impact of folinic acid rescue after methotrexate graft versus host disease prophylaxis on the incidence of mucositis, graft versus host disease, relapse and survival

• Outline the role of HCT pharmacists in the development of practice guidelines
Background

- MTX has additive toxicity
  - Mucositis
  - Hepatotoxicity
  - Delayed engraftment
- Only 62-73% receive day +11 MTX\(^1,2\)
- Omission of day +11 MTX increases risk of aGVHD\(^3,4\)

Background – How to Reduce Mucositis

- Reduced or omitted doses of MTX
- FA rescue
  - Limited data in HCT setting
  - Concern it may reduce MTX efficacy, therefore increasing the risk of aGVHD
  - Concern it may increase risk of relapse
- Supportive care management
  - Steroids
  - Opioids
  - Miracle mouthwash, topical anesthetics
  - TPN

HCT Pharmacist Role

- Assist in development and review of program guidelines and standard operating procedures
- Volunteered to review the data and present to the multidisciplinary HCT team
  - Rationale for FA use
  - Review of the literature
  - Present options and recommendations
  - Plan follow-up in 1 year, retrospective review
Rationale for Folinic Acid

- Canine unrelated histoincompatible BM graft
- No immunosuppression (IS) vs MTX + FA vs historical control (MTX only)
- Citrovorum factor 6 hours after each MTX dose
- MTX levels > $10^{-6}$ M completely abrogated thymidine uptake in lymphocytes on stimulation for 6 hours

Results
- MTX + FA dogs lived significantly longer than no IS
- Incidence of early deaths was significant in the MTX only group
- MTX + FA completely abrogated antibodies without signs of toxicity

Summary of Surveys

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>FA Use</th>
<th>FA Dose</th>
<th>FA Started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruutu 1997</td>
<td>81</td>
<td>46%</td>
<td>24 centers 1:1 MTX 11 centers: 3 to 15 mg/kg total dose</td>
<td>Started at 4, 6, 12, 24, 36 and 48 hours</td>
</tr>
<tr>
<td>Peters 2000</td>
<td>NR</td>
<td>85-90%</td>
<td>15 mg/m²/day</td>
<td>24 hours after each MTX</td>
</tr>
<tr>
<td>Bhurani 2008</td>
<td>18</td>
<td>66%</td>
<td>Dose 10 to 15 mg/m²</td>
<td>24 hours after each MTX</td>
</tr>
</tbody>
</table>

Reasons FA Utilized
- To avoid side effects such as:
  - Myelosuppression
  - Mucosal damage

Reasons FA not utilized
- No evidence of efficacy
- Possibility of increased risk of aGVHD

Summary of Literature

<table>
<thead>
<tr>
<th>N</th>
<th>MTX Dose (mg/m²)</th>
<th>FA Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres 1989</td>
<td>57</td>
<td>15/10/10/10</td>
<td>↓ toxicity G/VHD(NS)</td>
</tr>
<tr>
<td>Nevill 1992</td>
<td>82</td>
<td>15/10/10/10</td>
<td>↓ toxicity G/VHD/EFS(NS)</td>
</tr>
<tr>
<td>Russell 1994</td>
<td>69</td>
<td>15/10/10/10</td>
<td>5 mg q6h, 24 hr after MTX thru 12hr before next MTX G/VHD(NS)</td>
</tr>
<tr>
<td>Sugita 2012</td>
<td>118</td>
<td>15/10/10/10</td>
<td>↓ mucusitis G/VHD(NS)</td>
</tr>
<tr>
<td>Hudspeth 2013</td>
<td>47</td>
<td>15/10/10/10</td>
<td>↓ mucusitis RFS(NS)</td>
</tr>
</tbody>
</table>
Many Options for FA Use, No Consensus

- Patient Selection
  - Prophylaxis for all HCT
  - Prophylaxis for risk of severe mucositis only
  - Treatment if significant mucositis only
- Dose 5 mg to 15 mg/m²
- When to start – 6, 12, 18, or 24 hours
- Schedule and number of doses
  - Once after each MTX dose
  - q6h after each MTX dose
  - # of doses may vary due to time between

HCT Pharmacist’s Recommendation

- Myeloablative regimens only
  - CyTBI
  - VPCyTBI
  - Big BuFlu
  - BuCy and CyBu
- Leucovorin 10mg/m² IV q6h x 3 doses, starting 12 hours post each dose of MTX
- RIC, RT and NMA
  - Same as above only if severe mucositis with day +6 and/or +11 or at provider discretion

Methods

- Hypothesis – Utilizing FA after each dose of MTX will improve likelihood of administering day +11 MTX by reducing mucositis
- Compare pre-guideline (prior year 2012) with post-guideline implementation
  - Consecutive patients
  - Leucovorin 10 mg/m² IV q6h x 3 doses
  - Starting 12 hours post each dose of MTX
- Myeloablative regimens only
- First transplants only
Methods - Endpoints

- Primary endpoint (Statistical test: Chi-Square)
  - Ability to administer full dose day +11 MTX

- Secondary endpoints
  - Incidence (Statistical test: Chi-Square)
    - TPN and PCA use (Statistical test: Chi-Square)
    - Length of stay
    - Maximum grade mucositis (Statistical test: Mann-Whitney U)
  - Cumulative incidence (Statistical test: Log-rank)
    - aGVHD and cGVHD
    - NRM, Relapse and OS at 1 year

Patient Characteristics

Results – Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Pre-guideline</th>
<th>Post-guideline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Received day + 11 MTX 100%</td>
<td></td>
<td></td>
<td>0.0025</td>
</tr>
<tr>
<td>Reduced dose D3, D6 or D11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA 10mg IV q6h x 8 doses*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA added day +6 only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA added day +11 only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA added day +6 &amp; +11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 10mg flat dose
Results – Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Pre-guideline</th>
<th>Post-guideline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>27</td>
<td>0.9984</td>
</tr>
<tr>
<td>Mucositis Grade (Median)</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mucositis Grade 3/4</td>
<td>17 (54.8%)</td>
<td>10 (33%)</td>
<td></td>
</tr>
<tr>
<td>TPN</td>
<td>18 (58.1%)</td>
<td>13 (48.2%)</td>
<td>0.4499</td>
</tr>
<tr>
<td>Median TPN days</td>
<td>11 (range 5-55 days)</td>
<td>5 (range 3-13 days)</td>
<td></td>
</tr>
<tr>
<td>Median TPN Start Date</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>27 (87.1%)</td>
<td>17 (56.2%)</td>
<td>0.0500</td>
</tr>
<tr>
<td>Median PCA days</td>
<td>10.5 (range 6-54 days)</td>
<td>7 (range 3-13 days)</td>
<td></td>
</tr>
<tr>
<td>Median PCA Start Date</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Median LOS</td>
<td>27 (range 22-75 days)</td>
<td>24 (range 20-33 days)</td>
<td></td>
</tr>
</tbody>
</table>

48.4% of pre-guideline patients received some FA late, and post-guideline still better. Suggesting early FA use better.

Secondary Endpoints: GVHD

Secondary Endpoints: Relapse, NRM & OS
ARS

In this study, the use of folinic acid (FA) after each dose of methotrexate for the prevention of GVHD resulted in:

a) Increased use of TPN
b) Increased incidence of cGVHD
c) Increased ability to receive day + 11 MTX
d) Increased NRM
e) All of the above

Conclusions

• FA rescue after MTX for GVHD prophylaxis significantly improves the probability of administering day +11 MTX and reduces mucositis as evidence by significantly less utilization of PCA and a trend towards less TPN use without adversely impacting GVHD, relapse and survival
• The HCT pharmacist plays an important role in the review of literature, research, development of guidelines and education of the HCT team

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Special thanks to Dr. James Slack for his assistance with our program database and statistics.