Chapter 11: Regimen Related Toxicity

Purpose: The following guidelines are intended for patients in the BMT program who are experiencing regimen related toxicity.

Scope: These guidelines outline the treatment of regimen relate toxicity in patients who have undergone allogeneic hematopoietic stem cell transplantation at the University of Kentucky Markey Cancer Center.

I. Suggested Toxicity Criteria and Toxicity Reporting
II. Pulmonary toxicity-Interstitial Pneumonitis
III. Suggested Management of Diarrhea
IV. Pain Management
V. Approximate Oral and Parenteral Dose Equivalents
VI. Methadone Conversion Guide
I. Suggested Toxicity Criteria and Toxicity Reporting

A. Seattle (Bearman Criteria) (Appendix A). Specific protocols may represent exceptions to this.

B. Reporting Grade 3 and Fatal Transplant Related Toxicity to the QA/QI Committee

C. Reporting Toxicity to the QA/QI Committee: One function of the QA/QI Committee is to carry out audits of outcome among transplant patients. For this reason, episodes of grade 3 and fatal transplant related toxicity will be reported to this committee.

D. How toxicity will be reported:

1. The attending on service is responsible for immediately reporting such events to the data manager.

2. This will be done by filling out a “Report of Grade 3 or Fatal Toxicity” form (Appendix B). This will be passed on to the administrative head of the QA/QI committee with a copy also given to the Transplant Director.

3. The administrative head of the QA/QI will then pass the cases on to a physician, a nurse and Pharm D who are members of the committee to perform the function of reviewing these cases and briefly presenting them to the committee.

4. These presentations will be made quarterly and will include recommendations for changes in SOP’s or other procedures if appropriate.

5. Again, the goal is to improve patient care and prevent such episodes if possible. At the quarterly report, transplant related grade 3 and fatal outcome will be summarized for the year to date and will be broken down for autologous transplant, allogeneic transplant and matched sibling vs matched unrelated transplant.

6. This will be done by the data manager or by the physician responsible for reporting grade 3/fatal toxicity. Other relevant subgroups will be presented if adequate patient numbers exist.

E. Definition of Transplant Related Events

1. For autologous transplant these events are those related to the preparative regimen or resulting from treatment with that regimen.
   a) Therefore this includes events related to cytopenia such as infection or bleeding.
   b) Once relapse occurs in a patient with a hematologic malignancy, death from infection or bleeding are generally considered to be disease related.

2. For allogeneic transplant includes events related to preparative regimen AND mortality from GVHD and rejection.

II. Pulmonary Toxicity-Interstitial Pneumonitis

A. An acute/subacute pulmonary syndrome may occur in bone marrow or peripheral blood stem cell transplant patients who have received radiation and less commonly those who have received high-dose alkylating agent therapy.

B. Manifestations usually include shortness of breath, cough, hypoxia, and crackles on exam.

C. Evaluation should include CXR, followed by immediate high-resolution chest CT.

D. Particularly in patients who have undergone allogeneic transplant, BAL and transbronchial biopsy when possible should be performed expeditiously. In the meantime, empiric therapy for CMV, fungus and PCP should be considered.

E. High-dose corticosteroid therapy – 1000mg methylprednisolone in divided doses for 4-5 days may be given in the unusual setting of pneumonitis developing in the immediate post-radiation therapy setting.

F. In the more common situation of a patient who develops pneumonitis 1-3 months after transplant, treatment with 60-100 mgm of prednisone initiated as soon as symptoms develop should be considered. Again, bronchoscopy is advisable. Empiric therapy for pneumocystis and bacterial processes should be given if no bronchoscopy is performed.
III. **Suggested Management of Diarrhea**

A. Patients experiencing diarrhea will have intake and output documented including the number of stools per day, volume estimate and consistency.

B. These initial cultures will be obtained:

1. Stool Culture, Clostridium difficile Toxin (may be checked every 7 days as necessary) WBC, O&P, Rotavirus, Unknown Virus Cultures

2. For persistent diarrhea, consider additional studies

C. After the first set of initial cultures is negative the following therapy may be initiated:

1. Loperamide p.o. – 4 mg p.o. once – AFTER first loose stool
2. Loperamide p.o. – 2 mg p.o. – Begin after 4 mg one-time dose. May repeat after each loose stool with a maximum dose of 16 mg per day
3. Diphenoxylate/Atropine p.o. – 2 tablet(s) p.o. qid PRN - for diarrhea
4. Consider octreotide for diarrhea refractory to conventional treatment. (Barbounis 2001; Goumas 1998)

D. Treatment of Clostridium difficile patients includes:

1. Discontinuation of all anti-diarrheal medications and placement on isolation precautions
   Metronidazole 250 mg p.o. QID OR metronidazole 500 mg p.o. TID for 10-14 days
2. Vancomycin 125 mg PO QID for patients with the following indications:
   a) Documented allergy to metronidazole
   b) Diarrhea failing to respond to metronidazole
   c) Diarrhea that is severe and potentially life threatening (per HICPAC of the CDC).
3. Patients with persistent, culture negative diarrhea for greater than 7 days will have the following cultures obtained:
   a) Ova and Parasites
   b) Rotavirus Antigen (Stool)
   c) Cryptosporidium
   d) Microsporidium
   e) Giardia Antigen Procedure
   f) Cyclospora Procedure
   g) Unknown Virus Culture
   h) Stool WBC
   i) Miscellaneous Bacteriology –
   j) Test Name: Isospora Detection
   Consider endoscopy particularly in the setting of allogeneic transplant.

IV. **Pain Management**

A. Selecting an Appropriate Opioid and Route of Administration

1. Selection of an opioid agent(s) will depend on patient’s allergy status, pain intensity, and current analgesic therapy.
2. A balance between analgesia and side effects might be achieved by changing to an equivalent dose of an alternative opioid (see table 1 for equipotent dosing guide)
3. Commonly used agents: morphine (IV/PO/SQ/IM/SL), hydromorphone (IV/PO), fentanyl (transdermal), oxycodone (PO), and methadone (PO)
   a) For methadone conversion please refer to table 2.
   a) Due to its side effect profile, the use of meperidine should be limited to one time doses for treatment of chill/rigors or as sedation for procedures in patients with adequate renal function.
B. Adjuvant analgesics

1. Diverse drug classes used to manage bone pain, neuropathic pain, visceral pain and to reduce systemic opioid requirements
   a) Acetaminophen
   b) NSAIDs
   c) Tricyclic antidepressants (TCA)
   d) Gabapentin
   e) Anticonvulsant agents
   f) Bisphosphonates

<table>
<thead>
<tr>
<th>Opioid Analgesic</th>
<th>Oral Dose</th>
<th>Parenteral Dose</th>
<th>Duration of Action</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>15 mg</td>
<td>N/A</td>
<td>Q 3-4 hours</td>
<td>2.9 h</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>7.5-10 mg</td>
<td>N/A</td>
<td>Q3-4 hours</td>
<td>3.8 ± 0.3 h</td>
</tr>
<tr>
<td>Morphine</td>
<td>15 mg</td>
<td>5 mg</td>
<td>Q 3-4 hours</td>
<td>1.5-2 h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4 mg</td>
<td>0.75 -1.5 mg</td>
<td>Q 3-4 hours</td>
<td>2.5 h</td>
</tr>
<tr>
<td>Transdermal Fentanyl</td>
<td>N/A</td>
<td>50 mcg/h</td>
<td>Q 48-72 h</td>
<td>1-3 h</td>
</tr>
</tbody>
</table>

* Table adapted from the National Comprehensive Cancer Network, Adult Cancer Pain. Version 2.2005

<table>
<thead>
<tr>
<th>Total Oral Morphine Dose per day</th>
<th>Dose ratio (methadone : morphine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 90 mg morphine</td>
<td>1:4</td>
</tr>
<tr>
<td>90-300 mg morphine</td>
<td>1:8</td>
</tr>
<tr>
<td>&gt; 300 mg morphine</td>
<td>1:12</td>
</tr>
</tbody>
</table>

* Table adapted from Mercadante et al. JCO 2001; 19 (11) 2898-2904

§ The pain management guidelines are adapted from:

Mucositis

1. Definition: Short term, self-limited adverse effect causing disruptions in the function and/or integrity of the mucosal lining of the gastrointestinal tract that can be secondary to chemotherapy. (upToDate: oral toxicity assoc. with chemotherapy; Negrin 2011)
3. Symptoms: oral ulcerations, dysphagia and odynophagia, gastritis, diarrhea and malabsorption (Negrin 2011)
   a. Symptoms peak at day 7 (Negrin 2011)
4. Grading Scale per Bearman Criteria
5. Prophylaxis
University of Kentucky Markey Center
Patient Care Standards
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a. Salt and Soda oral rinse 4 times daily
b. Chew Ice 15 minutes before, during, and for 30 minutes following melphalan chemotherapy
c. Dental extraction in patient with poor dentition before transplant
d. Prophylaxis with acyclovir in patients with history of significant mucositis after chemotherapy.

6. Treatment
a. Continue salt and soda rises 4 times daily
b. Change patient’s po medications to IV as able to ensure compliance.
c. Pain management
   i. Lanny’s swish and swallow
      1. Give especially before meals
   ii. Po pain medications (i.e.: oxycodone, avoid oral meds with Tylenol combo)
   iii. IV pain medications (i.e.: morphine)
   iv. Pain PCA at direction of pain team with consult
d. Nutrition support
   i. Always encourage po intake as able.
   ii. Schedule medications iv or oral to be taken along with Lanny’s before patient attempts po nutrition
   iii. Feeding tube placement is discouraged secondary to concern for inflammation
   iv. TPN for patients unable to intake po
e. Airway Management
   i. Oral care per nursing
   ii. Oral suction encouraged to help with control of secretions
   iii. Intubation if patient with stridor, airway compromise.
      1. Important to alert/consult Pulmonary team before patients airway is to compromised to get secure airway.
f. Consider infectious cause for refractory mucositis and evaluate accordingly.

Hemorrhagic cystitis

1. Definition: Inflammation of the mucosal surface of the bladder and or ureters. (Moy 2011)
2. Symptoms: urgency, small volume frequency and dysuria, suprapubic pain
3. Occurs in 10-40% of patients receiving stem cell transplant (Ilhan 1997; Efros 1994)
4. Regimens placing patients at higher risk: cyclophosphamide and ifosfamide (ASCO 2009 Hensley) as well as radiation therapy (Crook 1996)
5. Categories
   a) Primary bladder cancer
   b) Infectious cystitis
   c) Direct antineoplastic injury
6. Grading scale per Bearman Criteria (See Appendix)
7. Prevention
   a) Mesna Fluids (ASCO 2009 guidelines)
   b) Hyperhydration with and after chemotherapy
   c) Careful attention to early symptoms
8. Evaluation and Diagnosis (Moy 2011)
   a) Check urinalysis and urine culture
   b) Send viral studies from urine (BK virus, CMV, adenovirus)
   c) Bladder Scan
   d) Urine Cytology
Hepatic Sinusoidal Obstruction Syndrome (VOD)

1. Definition: Liver injury characterized by symptoms listed below most commonly following patients undergoing stem cell transplantation. True etiology unknown.
2. Greatest risk of developing VOD is in first 3 weeks after transplantation (McDonald 1993)
3. Risk Factors:
   a. Preexisting liver disease (ie: chronic hepatitis)
   b. Conditioning chemotherapy prior to transplant including: Total body irradiation, Busulfan, cytarabine, cyclophosphamide, carmustine, etc. (McDonald 1993; Dix SP 1996; Morgan 1991; Lee 2005)
   c. Allogeneic at greater risk compared to autologous stem cell transplant recipients (McDonald 1993)
   d. Exogenous hormone therapy (Hagglund 1998)
4. Prophylaxis
   a. Lovenox 40 mg daily from admission to T+14 (Or R 1996)
   b. Actigall 600-900 mg/day (Essell 1992)
   c. T-cell depleted donor marrow (Soiffer 1992)
5. Symptoms:
   a. Hepatomegaly
   b. Right upper quadrant abdominal pain
   c. Ascites
   d. Sudden weight gain
   e. Increase in hepatic function testing (hyperbilirubinemia especially conjugated bilirubin)
6. Evaluation and Diagnosis
   a. Specific evaluation of fluid volume status with weights BID and strict I/O documentation
   b. Labs: CMP, direct and indirect bilirubin, PT/PTT
   c. Abdominal Ultrasound with measurement of portal-hepatic venous gradient
   d. Liver Biopsy for definitive diagnosis
7. Treatment
   a. Supportive care
      i. Diuresis with Lasix and/or spironolactone
      ii. Actigall can be used (Essell 1998)
      iii. Consider defibrotide study at other institution (Richardson 2002)

Nausea and Vomiting
1. Categories
   a. Immediate: N/V during administration of chemotherapy
   b. Delayed: N/V in first 3-5 days following chemotherapy
   c. Anticipatory: N/V related to a conditioned response to prior chemotherapy
2. Complications from uncontrolled nausea and vomiting
   a. Dehydration
   b. Electrolyte abnormalities
   c. Anorexia and malnutrition
   d. Poor quality of life
3. Treatment
   a. Prevention is best treatment. Prophylactic antiemetic regimens are based on the emetogenic potential of the patient’s chemotherapy regimen.
      i. Drugs include 5-HT3 antagonists, steroids, Emend (NK1 antagonist)
   b. Immediate Nausea/Vomiting
      i. 5-HT antagonist (Zofran, Kytral, Anzemet, Aloxi)
      ii. Steroids
      iii. Phenergan, Compazine
   c. Delayed Nausea/Vomiting
      i. Phenergan, Compazine
      ii. Emend
      iii. Reglan
      iv. Dexamethasone
      v. Aloxi
   d. Anticipatory Nausea/Vomiting
      i. Ativan
   e. Refractory Nausea/Vomiting
      i. Continue supportive therapy with IV fluids and electrolyte replacement.
      ii. Schedule traditional agents
      iii. Consider Marinol
      iv. Consider Zyprxa
      v. Scheduled low dose steroids
      vi. Cognitive behavioral therapy
      vii. Identify triggers and treat appropriately:
         1. Motion component: consider scopolamine
         2. Food trigger: consider scheduling low dose antiemetic therapy before meals.
         3. Dyspepsia: add or increase dose of PPI or H2 blocker.
         4. Esophageal symptoms: consider carafate
   f. Consider GI consult for endoscopy as indicated to evaluate for alternative causes i.e. GVHD vs. infection

Anorexia
1. Definition: loss of appetite or aversion to food that can be caused by conditioning chemotherapy regimen (Caringforcancer.org)
2. Causes
   a. Nausea/Vomiting
b. Ageusia  
c. Loss of appetite  
d. Diarrhea  
e. Mucositis  
f. Dysphagia  

3. Treatment  
   a. Encourage p.o. intake with frequent small meals  
   b. Control of nausea/vomiting/diarrhea/dysphagia  
   c. Dietary consult  
      i. P.o. Nutritional supplements (i.e: Ensure, high calorie Carnation protein shakes)  
   d. Pain control during period of mucositis  
   e. Medication for appetite stimulation: Marinol, Zyprexa, Remeron, Megace  

4. Treatment Failure  
   a. Alternative nutritional support  
      i. Dobhoff feeding tube as indicated  
      ii. TPN for acute management  
      iii. PEG tube for chronic management  
   b. Consider GI consult for endoscopy as indicated to evaluate for alternative causes ie. GVHD vs infection