CHEMOTHERAPY/BIOThERAPY-INDUCED HYPERSENSITIVITY REACTION: PREVENTION, MANAGEMENT AND RECHALLENGE

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Objectives

• Describe mechanisms of hypersensitivity reactions of anaphylactoid and anaphylactic reactions involved with different classes of chemotherapy/biotherapeutic agents
• Discuss management strategy in the event of hypersensitivity reaction
• Discuss factors that should be considered for rechallenge and understand how to apply desensitization protocol in clinical practice

Hypersensitivity Reactions (HSR)

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Description</th>
<th>Mechanism</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Immediate (&lt;1 h)</td>
<td>IgE-mediated, anaphylactic</td>
<td>Mast cells/basophils release &quot;vasoactive substances&quot;</td>
<td>Anaphylaxis, angioedema, urticaria, bronchoospasm</td>
</tr>
<tr>
<td>II</td>
<td>&lt;72 h</td>
<td>Cytotoxic (IgG/IgM-dependent)</td>
<td>Antigen/hapten-antibody complex</td>
<td>Hemolytic anemia, thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>III</td>
<td>&gt;72 h</td>
<td>Immune complexes</td>
<td>Antigen-antibody complex in vessels/tissues, causing Damage</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>IV</td>
<td>48-72 h</td>
<td>Cell-mediated or delayed HSR</td>
<td>Interaction with drug antigen and sensitized T-lymphocytes</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>V</td>
<td>&gt;72 h</td>
<td>Not well defined</td>
<td>T-cell toxicity</td>
<td>Maculopapular rash</td>
</tr>
</tbody>
</table>

Adverse Event

NCI Criteria for Adverse Events v.4.03 for HSR

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>Transient flushing, rash, drug fever &lt;38C. Intervention not indicated</td>
<td>Treatment interruption indicated</td>
<td>Anaphylactic, symptomatic bronchoospasm +/- urticaria, edema/angioedema, hypotension. Parenteral intervention indicated</td>
<td>Anaphylactic, Life-threatening consequences. Urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Cytokine-release syndrome</td>
<td>Mild reaction. Intervention not indicated</td>
<td>Treatment interruption indicated</td>
<td>Prolonged, or recurrence of symptoms following initial improvement, hospitalization indicated</td>
<td>Life-threatening consequences. Urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

Anaphylactic vs. -toid vs. Infusion reaction

<table>
<thead>
<tr>
<th>Anaphylactic reaction</th>
<th>Anaphylactoid reaction</th>
<th>Infusion-related reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immunologic</td>
<td>• Non-immunologic</td>
<td>• Any signs/symptoms developed during infusion</td>
</tr>
<tr>
<td>• IgE mediated</td>
<td>• Cytokine-mediated</td>
<td></td>
</tr>
<tr>
<td>(+) prior exposure to the antigen</td>
<td>± prior exposure to the antigen</td>
<td></td>
</tr>
</tbody>
</table>

Anaphylactic vs. -toid vs. Infusion reaction


Faculty Disclosures

• Served on Advisory Board for Sanofi-Aventis
Biphasic Anaphylaxis

- Up to 20% risk of recurrence within 72 h (usually within 8 h) after resolution of initial event

- Close monitoring necessary for up to 72 h following resolution of symptoms

Incidence of HSR

<table>
<thead>
<tr>
<th>Chemotherapeutic agents</th>
<th>Overall HSR</th>
<th>Severe HSR (G3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Asparaginase</td>
<td>5-25%</td>
<td>n/a</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Etopophosphorines 1</td>
<td>- Doxorubicin 1</td>
<td>- Up to 50%</td>
</tr>
<tr>
<td>- Teniposide 1</td>
<td>- 5%</td>
<td>- Rare</td>
</tr>
<tr>
<td>Isopodophyllotoxins 2</td>
<td>- Up to 5%</td>
<td>- 2%</td>
</tr>
<tr>
<td>- Up to 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutaxates 3</td>
<td>- Carboplatin</td>
<td>- Up to 9%</td>
</tr>
<tr>
<td>- Ciplatin</td>
<td>- 4%</td>
<td>- 2%</td>
</tr>
<tr>
<td>- 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 4</td>
<td>- 2%</td>
<td>- 12%</td>
</tr>
<tr>
<td>- 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Paclitaxel 4</td>
<td>- 21%</td>
<td>- 2%</td>
</tr>
<tr>
<td>- Albumin-bound Paclitaxel</td>
<td>- Up to 40%</td>
<td>- 2%</td>
</tr>
<tr>
<td>- Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus 5</td>
<td>- 9%</td>
<td>- 2%</td>
</tr>
</tbody>
</table>

1 Reserpine: Phosphate has been used as an alternative in case of HSR
2 Contains Polyethylene 90 as solvent
3 Contains Cremophor EL as solvent

More discussions on...

Asparaginase

<table>
<thead>
<tr>
<th>Product</th>
<th>Origin</th>
<th>Rate of HSR</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Asparaginase</td>
<td>E. Coli</td>
<td>≤5% per administered dose</td>
<td>≤3% by the 4th dose</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>E. Coli</td>
<td>≤10%</td>
<td>≤2% cross-sensitivity with L-Asparaginase, more severe vs. L-Asparaginase</td>
</tr>
<tr>
<td>Eraniya</td>
<td>Erwinia Chrysanthemi</td>
<td>Similar to L-Asparaginase</td>
<td>Cross-sensitivity with L-Asparaginase, E. Coli deriv is unlikely</td>
</tr>
</tbody>
</table>

Bleomycin

- Immediate/delayed “anaphylactoid” or “idiosyncratic reaction”, most commonly during 1st or 2nd treatment

- Pathophysiology: release of endogenous pyrogens (i.e. leukotriene and TNF) from the host cells, leading to endothelial cell damage

- Test dose required?
  - No uniform consensus - Correlation between dose and onset of the reaction unclear
  - Manufacturer recommendation:
    - Test dose ≤ 2 units IV for the first 2 doses in lymphoma patients. Monitor closely ≥ 1 h following test dose, then administer the remainder of the dose if no reaction observed
Hyperpyrexia syndrome:
- Febrile reactions (± wheezing, confusion, and hypotension)
- Sequelae: Disseminated Intravascular Coagulopathy, shock, multiorgan failure, and death have been reported

Hypersensitivity Pneumonitis & pulmonary fibrosis

Bleomycin

Platinums vs. Taxanes vs. mAb

<table>
<thead>
<tr>
<th>Platinums</th>
<th>Taxanes</th>
<th>mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents</td>
<td>Carboplatin, Cisplatin and Oxaliplatin</td>
<td>Paclitaxel and Docetaxel</td>
</tr>
<tr>
<td>Timing of reaction</td>
<td>Most commonly after 5 cycles</td>
<td>Usually within the first 10-15 min of the 1st or 2nd infusion</td>
</tr>
<tr>
<td>Mechanism of reaction</td>
<td>Anaphylactic reaction: Type I immune-mediated</td>
<td>Anaphylactoid reaction: from direct effect of a vehicle, drug or metabolite of drug on immune cells</td>
</tr>
</tbody>
</table>

Examples:
- Paclitaxel: Cremophor EL
- Docetaxel: Drug moiety

Which of the following agents is mostly likely to be associated with anaphylactic reaction after multiple treatments?

a. Paclitaxel  
b. Rituximab  
c. Carboplatin  
d. Docetaxel

Monoclonal Antibodies

Monoclonal Antibody

Cetuximab

- Associated with IgE-mediated anaphylactic reaction
- Derived from murine myeloma cell line, and expresses α-1,3-galactosyltransferase (oligosaccharide)
  - Note: Most of the other mAbs derived from Chinese hamster ovary cell line & do NOT express this enzyme
- (+) Exposure to oligosaccharide that is present on “Fab” portion of heavy chain IgE antibody production
- Prevalence of severe HSR vary in different regions of the US:
  - High rate (22%) in “Southeast” region (TN, NC, AR, MO, VA)
  - Low rate (<1%) in Northeast region
- Hypothesis: Association with exposure to regional pathogens?
Rituximab

- Fatal infusion-related reactions have been reported within 24 h of the infusion, mostly within 30 min.
- About 80% of the fatal infusion-related reactions occur with the first infusion.
- Overall incidence of infusion-related reactions during 1st vs. 4th vs. 8th infusions are 77% vs. 30% vs. 14%, respectively.
- Rituximab-associated infusion-related reactions have been known to be associated with cytokine release from the malignant lymphocytes.

Rituxan® (rituximab) package insert, Oct 2012

Mount Sinai Hospital Anaphylaxis policy
Anaphylaxis kit should be readily available by the treatment area during administration of chemo/biotherapy

MSMC Anaphylaxis Kit contains...

Step 1. Hold/Discontinue the offending agent

Step 2. Management
- Epinephrine (1:1000): 0.3 mg IM/SC q 5-15 min x 3-5 doses pm for airway obstruction or hypotension
  - (Add Glucagon 20-30 mcg/kg IV push to improve response to epi. in patients being treated with beta-blockers)
- O2: high flow rates
- Corticosteroid: MP 1-2 mg/kg IV for hypersensitivity reaction
- B-agonist: Albuterol neb/inh
- IV Fluid: 1-2 L isotonic crystalloid fluid ± vasopressor for hypotension
- Diphenhydramine: 25-50 mg IV

Step 3. Monitor for recurrence of anaphylaxis
- Close monitoring for up to 72 h after resolution of initial symptoms

In case of HSR...

Best Management Strategy is...

Prevention!

Published Desensitization Protocols

A) Platinums:
- Carboplatin
- Oxaliplatin

Published Desensitization Protocols

B) Taxanes:
- Feldweg AM, et al. Gynecol Oncol 2005;96::824-9

C) mAbs:
- Rituximab, Trastuzumab, Infliximab
- Cetuximab
- Panitumumab
  - Successful desensitization with cetuximab

D) L-Asparaginase

If a patient develops a mild HSR....

- Hold the infusion
- Administer following medications
  - Dexamethasone 20mg IV
  - Diphenhydramine 50mg IV
  - Ranitidine 50mg or Famotidine 20mg IV
- If the severity of reaction was mild-moderate, may rechallenge by reducing the infusion rate by 50%

Rapid Desensitization Protocol

- Developed by Brigham and Women’s Hospital
- Require 3- solutions with different conc in 250mL NS or D5W:
  - Bag 1: (X:100) mg
  - Bag 2: (X:10) mg
  - Bag 3: Xmg
- 12- step protocol
- Aim: gradually increase the infusion rate & drug concentration
- Total administration time: ~ 6 h
- First desensitization: in ICU with one to one nursing care.
  - Subsequent desensitizations: may be done in in regular oncology floor or in ambulatory setting, in one to one nursing care (if previous desensitization was successful)
Rapid Desensitization Process

- During desensitization process, both the surface IgE and FcRI are still present on the membrane.
- Q: Then why is there a lack of hypersensitivity reaction during desensitization?
- A: Stabilization of membrane-bound IgE receptors that carry the antigen being desensitized, leading to lack of mediators being released.

To Rechallenge or NOT to Rechallenge?

- How severe was previous reaction?
- Is the goal of therapy curative or palliative?
- Is there alternative therapy available?

SUMMARY

- Proper premedication is a key to prevent HSR
- Prompt recognition of HSR is a crucial initial step for management
- Anaphylactic kit should be readily available in the treatment area during the administration of chemo/biotherapy
- Decision to rechallenge should be based on multiple clinical factors and only if the benefit outweighs the risk
- Prior to rechallenge, in addition to appropriate antiemetics, premedicate with H-1 and H-2 blockers, and corticosteroid