Chemotherapy and Monoclonal Antibody Hypersensitivity: Evaluation and Management

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Disclosures

• None
Objectives

- Review common adverse/hypersensitivity reactions encountered with increased use of chemotherapeutics and monoclonal antibodies
- Provide effective tools to evaluate reactions to chemotherapeutics and monoclonal antibodies
- Discuss treatment strategies to manage reactions

Introduction

- Rapid expansion of the use of chemotherapeutics and biologics has resulted in an increase in hypersensitivity reactions
- All biologics have the potential to induce immunogenicity
  - Degree of humanization, pattern of glycosylation, episodic administration
**Allergy vs. Side Effect**

- Most side effects in chemotherapy are predictable such as hair loss, mucositis, nephrotoxicity, hepatotoxicity, ototoxicity, immunosuppression are caused by the chemotherapy affecting the non-cancerous “normal” cells in the body.

- Hypersensitivity reactions are not common, are unpredictable, and unrelated to the known pharmacologic reactions of the chemotherapeutic agent.

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**Incidence of Reactions**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Overall</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin (Paraplatin®)</td>
<td>2 %</td>
<td>none</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>15-20%, dependent on tumor type</td>
<td>3%</td>
</tr>
<tr>
<td>Docetaxel (Taxotere®)</td>
<td>5-12%</td>
<td>2%</td>
</tr>
<tr>
<td>Eloxatin (Oxaliplatin®)</td>
<td>15-33%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Paclitaxel (Taxol®)</td>
<td>41%</td>
<td>2%</td>
</tr>
<tr>
<td>Rituximab (Rituxan®)</td>
<td>77% First infusion, 30% fourth infusion, 14% eighth infusion</td>
<td>10%</td>
</tr>
</tbody>
</table>

Vogel, CJON 2010
Evaluation of a Patient with HSR

- Premedication
  - Steroids
  - Antihistamines
- Slowed infusion rates
- Desensitization

Decrease the Risk of a HSR

Brennan et al., JACI 2009
Carboplatin Hypersensitivity

- Ovarian cancer is the most fatal gynecologic malignancy
  - Majority of patients will develop recurrent ovarian cancer

- For women with recurrent ovarian cancer, repeat treatment with carboplatin is frequently recommended.
  - Increased risk of hypersensitivity reaction (HSR)
    - 1% with 6 or less exposures to carboplatin
    - Approximately 25% with 7 or more exposure

Incidence of hypersensitivity reactions in patients receiving Carboplatin

<table>
<thead>
<tr>
<th>Standard Infusion</th>
<th>Study</th>
<th>Type of Cancer</th>
<th>Frequency of HSR</th>
<th>Number of Previous cycles of carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Markman, M et al (1999)</td>
<td>Gynecologic</td>
<td>22/83 (27%)</td>
<td>7 Cycles or greater</td>
</tr>
<tr>
<td></td>
<td>Gaducci, A et al (2008)</td>
<td>Recurrent Ovarian</td>
<td>15/60 (25%)</td>
<td>6 cycles or greater</td>
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<tr>
<td></td>
<td>Schwartz, JR et al (2007)</td>
<td>Gynecologic</td>
<td>55/118 (47%)</td>
<td>Cycle 6-13 (mean cycle 9)</td>
</tr>
<tr>
<td></td>
<td>Caerbhail, R et al (2010)</td>
<td>Epithelial ovarian, fallopian tube, or primary peritoneal</td>
<td>111/555 (20%)</td>
<td>7 Cycles or greater</td>
</tr>
<tr>
<td></td>
<td>MGH Historical Data</td>
<td>Gynecologic</td>
<td>14/59 (24%)</td>
<td>7 Cycles or greater</td>
</tr>
</tbody>
</table>

Oxaliplatin Hypersensitivity

Park et al., JIACI 2016
Skin Testing for Platinum Agents

- Skin testing for platinum agents well-validated
  - Skin prick (epicutaneous) testing
  - Intradermal testing
- Patient must not receive anti-histamines for 5 days prior and should hold beta-blockers
- Patient has results same day

Is there a role for skin testing?

- 98-99% positive predictive value
- False negative rates as high as 8.5%

Carboplatin Desensitization is Safe and Effective

- >2000 successful desensitizations at MGH and BWH
- Majority tolerated without any reactions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Dose in each solution (mg)</th>
<th>Volume (ml)</th>
<th>Solution concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5</td>
<td>100</td>
<td>0.05 mg/ml</td>
</tr>
<tr>
<td>B</td>
<td>50</td>
<td>100</td>
<td>0.50 mg/ml</td>
</tr>
<tr>
<td>C</td>
<td>500</td>
<td>100</td>
<td>5.00 mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>Rate (m/s)</th>
<th>Time (min)</th>
<th>Administered dose (mg)</th>
<th>Cumulative dose (mg)</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>2</td>
<td>15</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>5</td>
<td>15</td>
<td>0.063</td>
<td>0.088</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>10</td>
<td>15</td>
<td>0.125</td>
<td>0.213</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>20</td>
<td>15</td>
<td>0.250</td>
<td>0.463</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>5</td>
<td>15</td>
<td>0.625</td>
<td>1.088</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>10</td>
<td>15</td>
<td>1.250</td>
<td>2.335</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>20</td>
<td>15</td>
<td>2.500</td>
<td>4.835</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>40</td>
<td>15</td>
<td>5.000</td>
<td>9.838</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>10</td>
<td>15</td>
<td>12.500</td>
<td>22.335</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>20</td>
<td>15</td>
<td>25.000</td>
<td>47.338</td>
</tr>
<tr>
<td>11</td>
<td>C</td>
<td>40</td>
<td>15</td>
<td>50.000</td>
<td>97.338</td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>75</td>
<td>64.4</td>
<td>402.663</td>
<td>500.000</td>
</tr>
</tbody>
</table>

Total time = 3.8 h, Total dose = 500 mg

Lee et al., Gynecol Oncol 2004
Lee et al., Gynecol Oncol 2005
Castells et al., J Allergy Clin Immunol 2008
Hesterberg et al. J Allergy Clin Immunol 2009

Mechanism of HSR to Carboplatin

- Exact mechanism remains unclear
  - Markman et al., suggest that the patient may be sensitized during first-line treatment (6 courses)
  - Retreatment with the same drug provides the additional immunological stimulation
- Felt likely to be IgE mediated
- Skin testing has been validated

Markman et al. J Clin Oncol 1999
Summary: Hypersensitivity to Platinum Agents

- Patient receiving multiple doses of platinum agents can become sensitized
- Consequently, these patients are often denied what is the best systemic therapy
  - results in the use of less effective second generation agents
- Skin testing is useful, but there remains a concern for false negative results
- Desensitization protocols have been successfully used to overcome HSR to platinum agents

Docetaxel and Paclitaxel Hypersensitivity

- HSRs to docetaxel and paclitaxel are primarily due to cremophor (polysorbate 80)
- HSRs occur in 30% of patients decreasing to <4% with premedication using antihistamines and steroids
- Reactions are dose- and rate-dependent and most often occur within the first few min of the 1st or 2nd infusions
- Symptoms include dyspnea, hypotension, bronchospasm, urticarial and erythematous rash
  - Clinical presentations similar to IgE mediated reactions
**Abraxane**

- There is a cross-reactivity rate of 90% between docetaxel and paclitaxel, therefore, substitution of the two is not recommended

- Cremophor-free formulations of albumin-bound paclitaxel decrease HSR risk

**Management of Paclitaxel HSRs**

- Slowed infusions
- Increase premedications
- Risk stratification
  - Allow patients to safely receive paclitaxel
  - Reduce the number of unnecessary desensitizations
Other Chemotherapeutic Agents

- **PEG-asparaginase**
  - Risk factors include IV admin, interval >1 week between admins and previous exposure to L-asparaginase

- **Procarbazine**
  - Type 1, 3 and 4 associated reactions with an incidence of 6% to 18%

- **Etoposide**
  - HSRs are thought to be caused by polysorbate 80
  - Can be prevented through adequate premedication and slow infusion rates

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Commonly Used Biologics

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Biologicals grouped according to their therapeutic principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Group</td>
<td>Examples</td>
</tr>
<tr>
<td>Cytokines</td>
<td>INF-α, GM-CSF</td>
</tr>
<tr>
<td>Monoclonal antibodies against</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>Infliximab (anti-TNF-α)</td>
</tr>
<tr>
<td>Cell surface molecules</td>
<td>Rituximab (anti-CD20)</td>
</tr>
<tr>
<td>IgE</td>
<td>Omalizumab (anti-IgE)</td>
</tr>
<tr>
<td>Tumor antigens</td>
<td>Cetuximab (anti-EGFR)</td>
</tr>
<tr>
<td>Fusion proteins</td>
<td></td>
</tr>
<tr>
<td>Soluble cytokine receptors</td>
<td>Etanercept (TNF-α-R1-IgG1)</td>
</tr>
<tr>
<td>Soluble cellular ligands</td>
<td>Abatacept (CTLA4-IgG1)</td>
</tr>
</tbody>
</table>

Hausmann et al., Med Clin N Am 2010
Evolution of Therapeutic Antibodies

- Murine: 100% Mouse protein
- Chimeric: 33% Mouse protein
- CDR-grafted: 5-10% Mouse protein
- Human Antibodies: 100% Human protein

Incidence of Infusion Reactions

- Rituximab: 77 cases
- Trastuzumab: 40 cases
- Cetuximab: 12.19 cases
- Panitumumab: 4 cases
- Bevacizumab: <3 cases
- Taxanes: 20-40 cases
- Platinum: 12.16 cases

Chung CH. Oncologist 2008
Classification of HSRs to Biologics

Mechanisms of Hypersensitivity Reactions

IgE and non-IgE mediated
Mechanisms of Hypersensitivity Reactions

Cytokine Release

- Monoclonal antibodies have a unique potential for a nonallergic infusion reaction caused by cytokine release
- Recognition and expert management of a cytokine-release reaction may enable patients to be rechallenged with the monoclonal antibody

Vultaggio et al., Curr Opin Allergy Clin Immunol 2011

Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment

Patrick J. Brennan, MD, PhD, *Tito Rodriguez Bouza, MD, *F. Ida Hsu, MD, David E. Sloane, MD, and Mariana C. Castello, MD, PhD Boston, Mass

A Initial reactions

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab</th>
<th>Infliximab</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3)</td>
<td></td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>(6)</td>
<td>40</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>(14)</td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

% of patients

B Reactions during desensitization

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab</th>
<th>Infliximab</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>(29)</td>
<td></td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>(21)</td>
<td>40</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>(55)</td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

% of desensitizations

Brennan et al., JACI 2009
Management of Reactions during Desensitization

Case: Hypersensitivity Reaction to Rituxan

- JM is a 72 year old male recently diagnosed with Non-Hodgkin’s Lymphoma, started on Rituxan therapy
- About one hour after starting his first infusion, he developed fever, chills and back pain
- Infusion was stopped and he received IV diphenhydramine and ranitidine
  - symptoms resolved within 35 minutes
- He refused rechallenge and presents today for your advice
How do you evaluate JM’s symptoms as a possible hypersensitivity reaction to Rituxan?

**Rituxan Hypersensitivity**

- Chimeric murine/human mAb against CD20 on normal and malignant B lymphocytes
- Infusion reactions with fever, chills and rigor reported in 5-10%
- Usually first dose within 30 minutes to 2 hours
  - correlate with disease burden and decrease with subsequent infusions
- Often resolve with slowing of the infusion
- Most reactions are not thought to be IgE-mediated

Grillo-Lopez et al., Semin Oncol 1999
Dillman et al., 1999
Mechanisms for Hypersensitivity to Rituxan

- **Cytokine Release Syndrome**: fever, chills, nausea, vomiting, hypotension, dyspnea
  - Increased serum TNF, IL-6

- **Tumor Lysis Syndrome**: renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia
  - Usually within 12-24 hours of infusion

- **Pseudoallergic Reactions**: urticaria, bronchospasm, hypotension, flushing

Rituxan Skin Testing

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicutaneous</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Intradermal</td>
<td>0.1 mg/mL</td>
</tr>
<tr>
<td>Intradermal</td>
<td>1 mg/mL</td>
</tr>
</tbody>
</table>

- Performed at specific academic centers
- Little data on sensitivity and specificity with poor predictive value currently
- Reaction rate lower during desensitization in ST negative patients but reactions seen in both skin test positive and skin test negative patients

*Mechanism of hypersensitivity is unclear*

Brennan et al. JACI 2009
Management of Patients with HSR to Rituxan

- 23 patients underwent 105 successful desensitizations

A Initial reactions

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab (3)</th>
<th>Infliximab (6)</th>
<th>Rituximab (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>60%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Moderate</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Severe</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

B Reactions during desensitization

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab (29)</th>
<th>Infliximab (21)</th>
<th>Rituximab (55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Reaction</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Mild</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Moderate</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Severe</td>
<td>10%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Rituximab Risk Stratification

- Infusion Reaction
  - Grade 1
    - Same Day Rechallenge
  - Grade 2 OR history of Grade 1
    - Intermediate Desensitization x2
      - Further Reactions
    - Tolerated
  - Grade 3 or 4
    - Intermediate Desensitization
      - Further Reactions
    - Tolerated
- Rapid Desensitization
  - 50% Infusion Rate (Inpatient)
    - Tolerated
  - 50% Infusion Rate (Outpatient)
    - Tolerated
    - Further Reactions
**Infliximab**

*Chimeric Monoclonal Antibody TNFα*

- Acute infusion reactions
  - Within 10 minutes to 4 hours
  - Can often continue with slowed infusions/premedication
  - With more severe reactions, desensitization has been successful

- Delayed infusion reactions
  - Usually 5-7 days later
  - Arthralgias, fevers, malaise, urticaria, myalgias, “serum-sickness” like

**Antibodies to Infliximab**

- Antichimeric antibodies (ATIs) are produced in a substantial number of patients

- Positive correlation between ATIs and both acute and delayed infusion reactions along with reduced efficacy of treatment
  - Concomitant administration of methotrexate reduces antibodies

- Not all patients with ATIs suffer from infusion reactions suggesting a role for other cofactors

- Shifting to another TNFα antagonist generally tolerated
Serum Anti-Chimeric Antibodies: Infliximab

Vultaggio et al. Allergy 2010

Cetuximab

- Chimeric IgG1 monoclonal antibody EGFR
- HSRs reported in 1-22% of patients
  - Higher rates in certain regions
- HSR frequently reported within minutes of initial exposure
- Found to be related to antibodies specific for galactose-α-1,3-galactose present on Fab portion of cetuximab
IgE Antibodies Binding to Cetuximab

Summary

- Approach will vary by drug and mechanism of hypersensitivity
  - Discontinue drug and use reasonable alternative
  - Slowed infusion
  - Pre-medication regimen
  - Skin Testing
  - Induction of tolerance
  - Utility of risk stratification