Cancer Chemotherapy Desensitization for the Treatment of Drug Hypersensitivity Reactions

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Harvard Medical School
Director, Adverse Drug Reactions and Desensitization Program

Complex Allergies

• Cancer patients survive longer and are exposed to multiple chemotherapy treatments

• Patients with chronic inflammatory diseases (RA, IBD, Psoriasis) are repeatedly exposed to new monoclonal Abs and other biological agents

• Patients with cystic fibrosis survive longer, receive lung transplants and are exposed to multiple courses of antibiotics

• Increase in Atopic diseases
Allergy Therapy Mechanisms

I. Classical Immunotherapy
   Thr, IgG4
   months to years
   pollen, dust mites, other allergens

II. Rush Immunotherapy
    Syk
    weeks to months
    hymenoptera venom, specific pollen

III. Rapid desensitizations
    hours to days
    chemotherapy, antibiotics, monoclonals,
    aspirin, foods (peanut, milk, others)

Hypersensitivity Reaction to Carboplatin
Anaphylactic IgE

- 49 year old female with ovarian cancer
- Treated with Taxol and carboplatin x 6 cycles with no side effects
- Recurrence of cancer, restarted on Taxol and Carboplatin for 6 more cycles
- 2nd infusion with Carboplatin (8 cycle): cramping, abdominal pain,
  flushing/pruritus, diffuse urticarial rash, SOB, hypotension, code
- Skin test to carboplatin: positive
Incidence of Carboplatin HSR

• patients receiving > 7 cycles of carboplatin have 27% of HSR, and 50% of those patients develop moderate to severe symptoms (anaphylaxis).

• Increased pre-medication (steroids) and re-infusion does not prevent HSR reactions.

• Cross-reactivity among platins is high.

Adverse Reaction to Rituximab
Anaphylactic : IgE / non-IgE

• 38 yo male with non-Hodgkin lymphoma

• 1st infusion of rituximab : 15 min

• Severe itching, nausea, dizziness, SOB, hypotension, collapse

• Skin test : negative
How to overcome IgE and non-IgE mediated anaphylactic reactions?

- Avoidance
- Substituting
- Control/Inhibition mast cell/IgE reactions

**Rapid Desensitization:**
- No substitute
- Life-threatening
- Less efficacy

Rapid Desensitization

Rapidly (hours) inducing a state of temporary tolerance / tolerization to a medication / food to which a patient had presented a severe hypersensitivity / anaphylactic reaction
Evolving concepts

- **High risk procedure**: requires the introduction of a potentially lethal medication to a highly sensitized patient
- **Performed in critically ill patients**: survival depends on administration of a medication to which a patient has a previous history of a severe adverse reaction
- **No alternative medications** are available or the alternatives (second and third line choices) have less demonstrated therapeutic value than first line treatment

Current understanding

- It is a **temporary** phenomenon
- **Antigen specific**, not IgE depleting, not hapten inhibition nor depletion of mast cell mediators
- It is done by **repetitive increasing sub-optimal doses (suboptimal concentrations)** of the medication involved in the adverse reaction
- Once desensitization is complete, the tolerization can be **maintained** by continuous administration of the medication
- **Can only be done by trained allergists**
Cellular targets

- Mast cells:
  positive skin test
  negative after desensitization

- Side effects:
  10-30% of patients
  consistent with mast cell/basophil mediators release

Effect of desensitization on skin test reactivity

Table 4.
Effect of desensitization on skin test reactivity: wheal/flare (mm) response for Patient 10

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Carboplatin</th>
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<tr>
<td></td>
<td>Histamine (prick)</td>
<td>Dibenz (intradermal)</td>
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<tr>
<td>Before desensitization</td>
<td>positive (5/15)</td>
<td>negative (4/0)</td>
</tr>
<tr>
<td>After desensitization</td>
<td>positive (4/13)</td>
<td>negative (4/0)</td>
</tr>
</tbody>
</table>

* Wheat produced by carboplatin (intradermal) versus wheal produced by histamine (prick).

Lee ChW, Matulonis UA, Castells MC; Gyn Onc Nov 2004
Mediators released from activated mast cells

Human Mast Cells

Tryptase/Chymase  Tryptase
Proposed Mechanisms for Rapid IgE/Antigen Desensitizations

- **Monovalent** (monomeric) antigen can bind IgE/FceRI but block the activation and release of mediators (Paolini R, PNAS 1992)
- **Internalization** of Antigen/IgE/FceRI units (Rubinchick E, 1998)
- **Inhibitory Receptors** on Mast Cells (Katz H, Castells M, 2001, 2003)
- **Reduced Expression of Syk Protein Tyrosine Kinase** (MacGlashan 2004 and Kepley 2004)

Inhibition of FcεRI-induced mast cell activation by LILRB4

Tyrosine Phosphorylation/Activation of Lyn, Syk, PLC-γ    SHP-1  Mast Cell activation

Castells et al. Nature Immunology 2001
Rapid desensitization blocks the release of pre-formed mediators

Desensitization to DNP-HSA

Desensitization to OVA

Duration of rapid desensitization

As long as the desensitizing antigen is present mast cells remain desensitized
Desensitization impairs calcium influx and is specific

Cells desensitized to one antigen (DNP) respond to a challenge with a second antigen (OVA)

Molecular targets of rapid desensitization

Antigen-IgE desensitization in a signal transducer and activator of transcription 6-deficient mast cells by suboptimal doses of antigen.

Rodriguez Morales, A., Shah, N., Castells M.  
Ann Allergy Asthma Immunol  
May 2005
Antigen is not internalized during rapid desensitization

CONCLUSIONS:

IgE Rapid Desensitization:

- inhibits β-hexosaminidase release and extracellular calcium entry (no mediator depletion)
- is an antigen specific process
- can be maintained in the presence of antigen
- inhibits STAT6 and LAT phosphorylation
- inhibits Antigen FcRl / IgE receptor internalization
From In Vitro Model to In Vivo Rapid Desensitization for IgE-mediated reactions

- Starting Dose
- Dose escalation
- Time between doses
- Threshold
- Mediator Release

What protocol should be used?

BWH Standard Protocol for Rapid Desensitization

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Total time = 351 minutes

*note to pharmacy*: The total mg injected is more than the final dose because solutions 1 and 2 are not completely infused.
Who is a candidate for Rapid Desensitization?

- No age limitations
- Informed consent
- Type I hypersensitivity reaction (anaphylaxis)
- Positive skin test

**Exclusion criteria:**
- Type III or Type IV reactions
- Steven’s Johnson Syndrome
- Toxic Epidermal Necrolysis
- ACE-induced angioedema

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**Risk Stratification**

**Low Risk**
- FEV1 > 1.5 L
- No cardiac history
- Mild reaction

**High Risk**
- FEV1 < 1.5 L
- Cardiac Disease w/wo beta blockade
- Severe reaction: anaphylaxis/intubation
Drugs used in Rapid Desensitizations BWH

- **Chemotherapy agents**
  - Platins (carboplatin, cisplatin, oxaliplatin)
  - Taxanes (paclitaxel, docetaxel)
  - Doxorubicin/Adriamycin, cytoxan.

- **Monoclonal antibodies**
  - rituximab, trastuzumab, adalimumab.

- **Antibiotics**
  - ancef, bactrim, ceftazidime, ceftriaxone, cefazolin, ciprofloxacin, ertapenem, imipenem, meropenem, nafcillin, penicillin, piperacillin, trimethoprim, unasyn, zosyn.

- **Aspirin/NSAIDs**
  - aspirin, allopurinol

Clinical Symptoms amendable to Rapid Desensitization

Castells et al JACI 2008
Desensitization Step at which reactions occurred

Castells et al. JACI 2008

Desensitization Course at which reactions occurred

Castells et al. JACI 2008
Safety of Rapid Desensitizations 413 cases
Castells et al. JACI 2008

- No Reaction: 67% (278/413)
- Mild Reaction: 27% (111/413)
- Severe Reaction: 6% (24/413)

94% of cases with mild or no reactions

Effectiveness of Rapid Desensitizations

100% of patients completed desensitization protocol at BWH in 2005-2006:

- 413 cases chemotherapy
- No Codes, No Deaths

Castells et al. JACI, 2008
Background: Rapid desensitization, a procedure for graded drug administration, allows for the safe readministration of a medication after certain types of hypersensitivity reactions (HSRs) and is indicated in cases in which there are no reasonable therapeutic alternatives. The use of rapid desensitization for HSRs to mAbs has not been validated.

Objective: We sought to describe our experience with rapid desensitization to mAbs, including rituximab, infliximab, and trastuzumab.

Methods:
One hundred five rapid desensitizations were performed in 23 patients with a standardized 12-step, 6-hour protocol. Our approach to patient evaluation before desensitization is described. The severity, characteristics, and timing of both initial HSRs and HSRs during desensitization were determined by means of retrospective review of medical records. After a reaction during desensitization, patient-specific protocol modifications were made before each subsequent desensitization.
Protocol for monoclonal Ab desensitization

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<th>Table</th>
<th>Desensitization protocol for intravenous infliximab (500 mg)</th>
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Total time = 300 min (5 hrs)


New biological agents: Evaluation of patients for desensitization to monoclonal Abs

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

Patient Characteristics for monoclonal Ab desensitization

<table>
<thead>
<tr>
<th>Agent</th>
<th>Age/sex</th>
<th>Indication</th>
<th>Atopy</th>
<th>Reaction</th>
<th>Skin test result</th>
<th>No. of desensitizations</th>
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Severity of initial reactions and reactions during desensitization

Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment.
Characteristics of initial reactions and reactions during desensitization.

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

Step at which reactions occur during monoclonal AB desensitization

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

Results: 104 of 105 desensitizations undertaken were successfully completed. We observed HSRs during 29% of desensitizations, including 27 mild reactions, 1 moderate reaction, and 2 severe reactions. Overall, reactions during desensitization were markedly less severe than initial HSRs, but reactions did recur in a minority of successive desensitizations.

Conclusions: Rapid desensitization is a promising method for the delivery of monoclonal therapeutics after an HSR, but the possibility of a reaction remains with each desensitization.

Management for hypersensitivity reactions to mAb during rapid desensitization

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

Acetylsalicylic acid and montelukast block mast cell mediator–related symptoms during rapid desensitization
Rebecca G. Breslow, MD*; Joana Caiado, MD**; and Mariana C. Castells, MD, PhD* 2009
CF patients often demonstrate hypersensitivity to one or multiple antibiotics due to frequent and repeated exposures. Attempts at antibiotic desensitization in this population are historically complicated by higher reaction rates, failure to complete the procedure and consequent withholding of first-line therapy.

- **Methods:** We retrospectively reviewed the medical records of 15 patients undergoing 52 rapid antibiotic desensitizations at Brigham and Women's Hospital and Children's Hospital Boston utilizing our protocol.

- **Results:**
  - Mean FEV1 % predicted was 44.1 (SD 16.5), with two patients at 30% and one patient desensitized during bilateral lung transplantation.
  - Adverse reactions during desensitization occurred in 13.4%, and most were mild.
  - 100% of patients completed the protocol and ultimately tolerated subsequent full-strength antibiotic courses.

- **Conclusions:** CF patients with antibiotic hypersensitivity can safely receive first-line antibiotics via our rapid desensitization protocol, including those with severe obstructive lung disease.
Cefepime Desensitization in CF

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<th>Time (min)</th>
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Total time: 242.23 minutes (4h 4.23 min)

A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity

Henry J. Legere III a,1, Ross I. Palis a,1, Tito Rodriguez Bouza a,1, Ahmet Z. Uluer a,*, Mariana C. Castells a,*

a Brigham and Women’s Hospital, Harvard Medical School, Division of Rheumatology, Immunology and Allergy, 75 Francis Street, Boston, MA 02115, United States.

Received 31 May 2008; revised 21 June 2009; accepted 4 August 2009.

1. Antibiotic desensitizations in CF patients are safe.
2. We report 100% successful administration of antibiotics utilizing the BWH desensitization protocol.
3. Lung function, as measured by FEV1, or transplant status is not a contraindication to desensitization.
4. Allergists should match the final concentration of the desensitization antibiotic solution to that of the concentration typically administered to non-allergic patients in order to maximize tolerance to the subsequent full-strength antibiotic course.
Selected Publications


Thank you to the Ovations for the Cure Desensitization Program!!!!