Mechanisms of Hypersensitivity Reactions Associated with Chemotherapeutic Agents and Biologicals

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DISCLOSURES

- No financial relationships to disclose

LEARNING OBJECTIVES

Upon completion of this learning activity, you should be able to…

- Identify* the pathobiology of hypersensitivity reactions (HSRs) to chemotherapeutic agents and biologics.
- Clarify* how the clinical presentations of patients experiencing HSRs to chemotherapeutic agents and biologics suggest possible pathobiologic processes underlying such reactions to these agents.

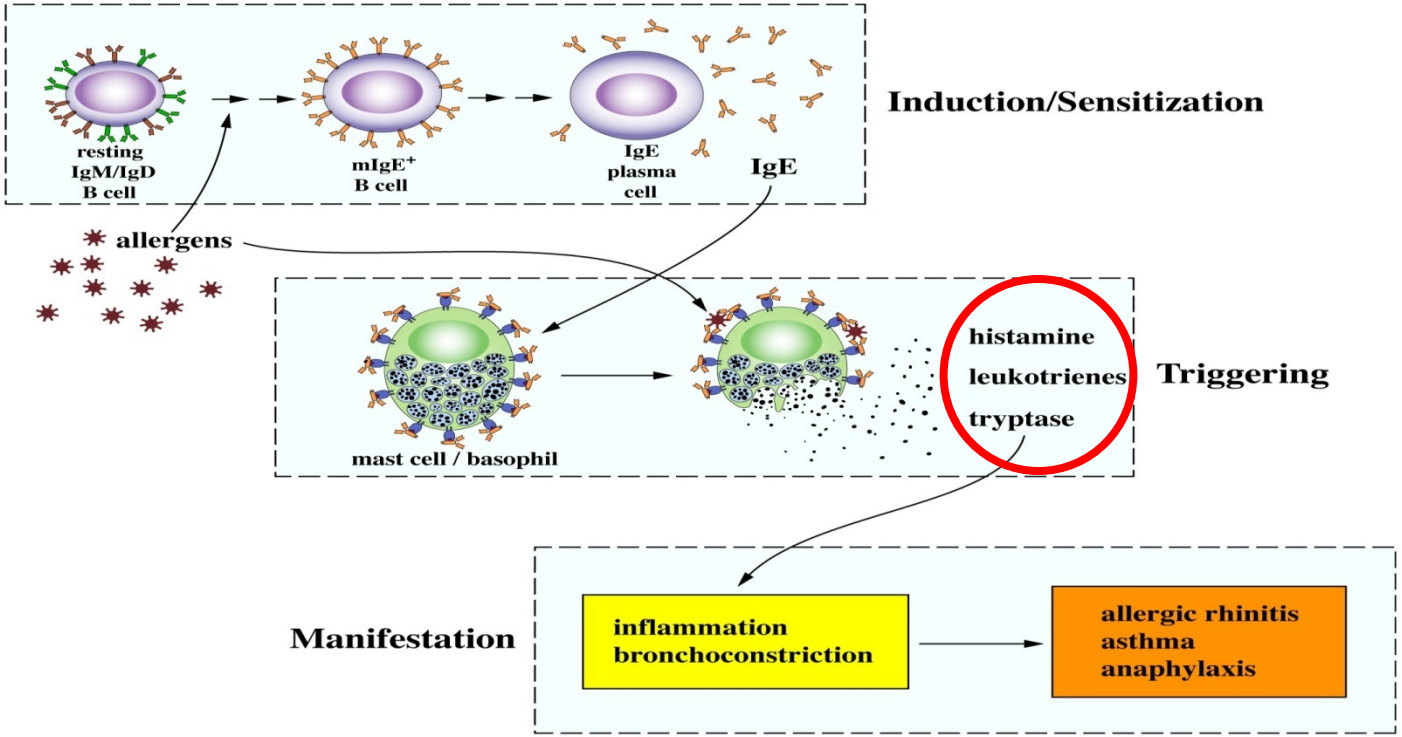
Schema

- Drug
- Indication(s) (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)
- Reaction phenotype (symptoms and signs)
- Mechanism

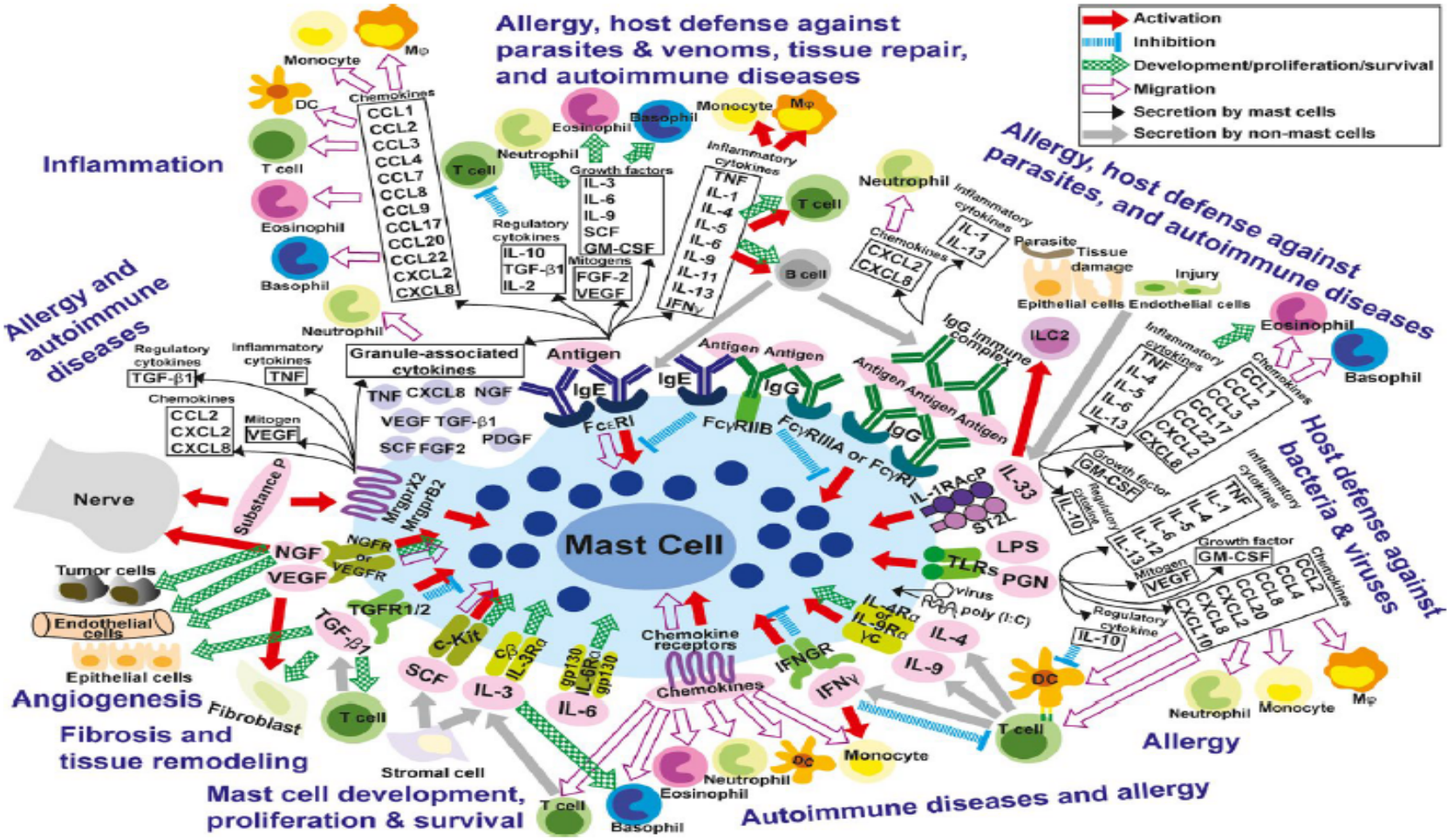
Heterogeneity, Complexity, and Ignorance

- "The answer is: it depends."
  - Julian Seifter *After the Diagnosis*
- "The final result is thus rendered infinitely complex."
  - Charles Darwin *On the Origin of Species by Natural Selection*
- "Teach your tongue to say 'I do not know.'"
  - Babylonian Talmud *Brachot* 4a

What we're used to thinking about: the Mast Cell + IgE Paradigm



Slide courtesy of Dr. Tse Wen Chang


Activation
Inhibition
Development/proliferation/survival
Migration
Secretion by mast cells
Secretion by non-mast cells
Allergy, host defense against parasites & venoms, tissue repair, and autoimmune diseases
Inflammation
Allergy and autoimmune diseases
Allergy, host defense against parasites, and autoimmune diseases
Host defense against bacteria & viruses
Mast Cell
Nerve
Tumor cells
Endothelial cells
Epithelial cells
Angiogenesis
Fibrosis and tissue remodeling
Mast cell development, proliferation & survival
Autoimmune diseases and allergy
Allergy
Monocyte
Mφ
DC
T cell
Eosinophil
Basophil
Neutrophil
B cell
ILC2
Fibroblast
Stromal cell
Chemokines
Growth factors
Inflammatory cytokines
Regulatory cytokines
Mitogens
Granule-associated cytokines
Antigen
IgE
IgG
IgG immune complex
FcεRI
FcγRIIB
FcγRIIIA or FcγRI
Substance P
MrgprX2
MrgprB2
NGF
VEGF
NGFR or VEGFR
TGFR1/2
TGF-β1
c-Kit
IL-3Rα
gp130
IL-6Rα
SCF
IL-3
IL-6
Chemokine receptors
IFNGR
IFNγ
IL-4Rα
IL-9Rα
γC
IL-4
IL-9
IL-1RAcP
ST2L
IL-33
TLRs
LPS
PGN
virus
poly (I:C)
Parasite
Tissue damage
Injury
Epithelial cells
Endothelial cells
CCL1
CCL2
CCL3
CCL4
CCL7
CCL8
CCL9
CCL17
CCL20
CCL22
CXCL2
CXCL8
CXCL10
IL-10
TGF-β1
IL-2
FGF-2
VEGF
TNF
IL-1
IL-4
IL-5
IL-6
IL-9
IL-11
IL-13
IFNγ
GM-CSF
PDGF
SCF
FGF2
CXCL8
NGF

Taxanes

- Paclitaxel and albumen-bound paclitaxel
  - indications = ovarian carcinoma, node positive breast cancer, non small cell lung cancer (NSCLC), AIDS-related Kaposi's sarcoma
  - albumen-bound indications = metastatic breast CA, NSCLC, metastatic pancreatic adenocarcinoma
- Docetaxel
  - indications = breast CA, NSCLC, castration resistant prostate CA, gastric adenocarcinoma, squamous cell carcinoma of the head and neck

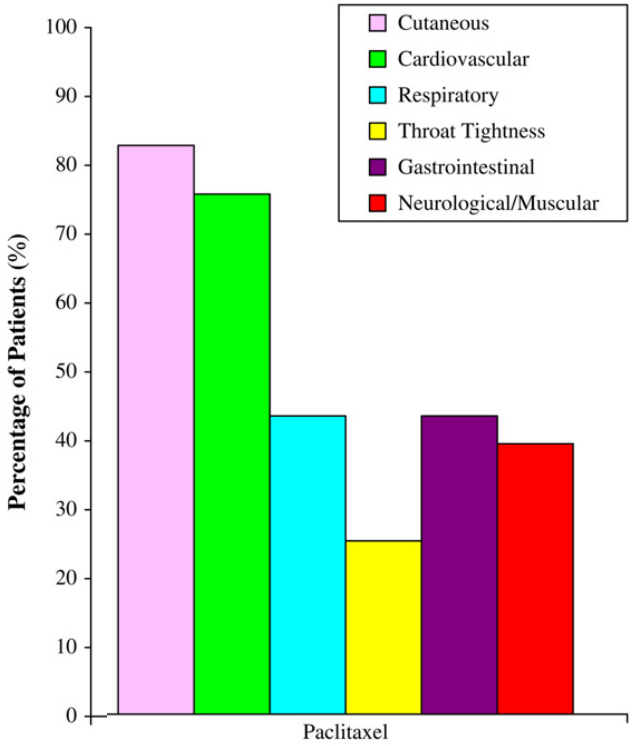
Paclitaxel: FDA Boxed Warning

- "Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving [paclitaxel] in clinical trials. Fatal reactions have occurred in patients despite premedications. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists (See **DOSAGE AND ADMINISTRATION.**) Patients who experience severe hypersensitivity reactions to [paclitaxel] should not be rechallenged with the drug."

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf

Paclitaxel

- Cutaneous
  - flushing, pruritus, urticaria ± angioedema, maculopapular rash
- CV
  - Chest pain, tachycardia, sense of impending doom, presyncope, syncope, HTN, hypoTN
- Respiratory
  - Sneezing, nasal congestion, dyspnea, cough, wheezing, O_2 desaturation
- GI
  - Nausea, vomiting, diarrhea, abd pain, bloating
- Neuromuscular
  - disorientation, hallucinations, visual changes, ear ringing/pounding, unusual taste, back pain, numbness, weakness.



Paclitaxel

- Polyoxyl 35 castor oil or Cremophor reactions
- Often occur on the first or second lifetime exposure
- Mechanism = ? Direct mast cell activation, ? complement activation, ? previous sensitization with cremophor specific IgE.

- Paclitaxel reactions (albumen-bound paclitaxel)
- Much rarer than the cremophor version of paclitaxel
- Mechanism = may be IgE mediated mast cell activation.

Platinum-based agents

- Carboplatin
  - indication = ovarian carcinoma
- Cisplatin
  - indications = advanced ovarian, testicular, or bladder cancer
- Oxaliplatin
  - indications = stage III colon cancer/advanced colorectal cancer

Carboplatin (and Cisplatin)

- Cutaneous
  - flushing, pruritus, urticaria ± angioedema, maculopapular rash
- CV
  - Chest pain, tachycardia, sense of impending doom, presyncope, syncope, HTN, hypoTN
- Respiratory
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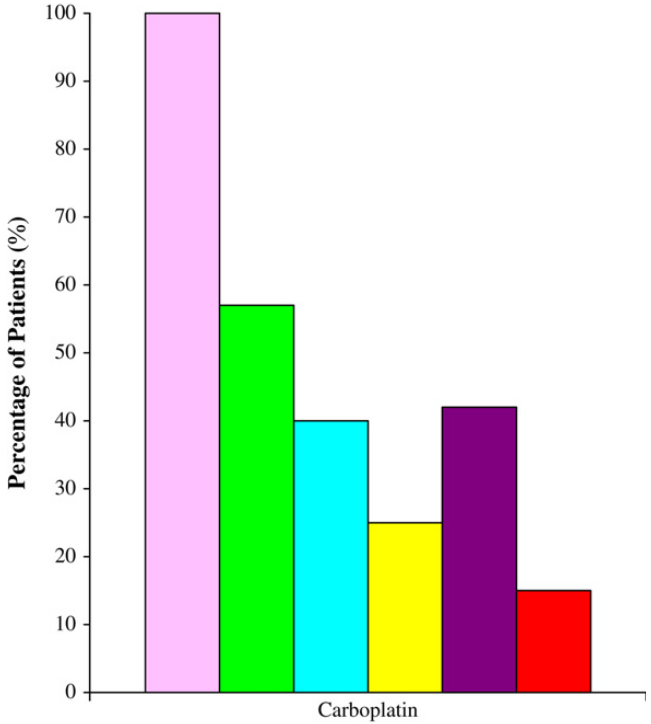

Carboplatin

- Generally occurs between lifetime exposures 6-9.
- Rate = approx 2% of patients with anaphylactic-type reactions
- Mechanism: Carboplatin specific IgE has been demonstrated in a study of 5 patients with ovarian CA and carboplatin HSR, and pretreatment with omalizumab appears to be effective in at least some of these patients.

Oxaliplatin

- Causes a variety of reactions along a gamut of time courses and severities.
- Rate = 32/169 patients (19%) in one retrospective study
  - Gowda A *et al*. Hypersensitivity to Oxaliplatin: Incidence and Management. Oncology 2004;18(13):1671-1675.

Cytokine release reactions

- Manifestations = rigors, fever, oxygen desaturation,
- May be acute or delayed (minutes to hours)
- Elevated serum IL-6 concentrations, and sometimes TNF-α. Source cells as yet unknown.

Thrombocytopenia

- Can be profound (undetectable PLT count) and lead to serious hemorrhagic manifestations.
- Still at the case report level, though FDA trials reported 2-5% depending on whether 5-FU and leucovorin were co-administered.
- Appears to be due to multiple drug specific antibodies, such as anti-GP1b/IX, but patients are predisposed to produce other drug specific anti-platelet antibodies (e.g., anti-dexamethasone,-irinotecan, -leucovorin, -diphenhydramine(!))
- Oxali metabolites can covalently bind to macromolecules, and may do so to the CDR of some antibodies increasing their binding capacity for platelet surface glycoproteins.
- Curtis BR, *et al.* Patients treated with oxaliplatin are at risk for thrombocytopenia caused by multiple drug-dependent antibodies. Blood 2018;131(13):1486-1489.

Biologics (a few of many)

- Brentuximab = anti-CD30 conjugated to vedotin
  - indications = classical Hodgkin's Lymphoma, systemic anaplastic large cell lymphoma, peripheral T cell lymphoma, primary cutaneous anaplastic large cell lymphoma or mycosis fungoides.

- Trastuzumab = HER2/neu receptor antagonist
  - indications = metastatic breast CA, metastatic gastric or gastroesophageal junction adenocarcinoma

- Bevacizumab = anti-vascular endothelial growth factor
  - indications = metastatic colorectal CA, non-squamous NSCLC, Glioblastoma, metastatic renal cell carcinoma, cervical CA, epithelial ovarian/fallopian/primary peritoneal cancer

Biologics (cont.)

- Rituximab = anti-CD20
  - indications = Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (GPA) or Microscopic Polyangiitis, Pemphigus Vulgaris (PV)

- Infliximab = anti-TNF
  - indications = Crohn's Disease, Ulcerative Colitis, RA, Ankylosing Spondylitis, Psoriatic Arthritis (PSA), Plaque Psoriasis

Biologics

- Pilcher and Campi classification of adverse side effects of biological agents
  - **α = elevated cytokine concentrations**
  - **β = hypersensitivity due to immune reaction to the biologic agent**
  - γ = immune or cytokine imbalance
  - δ = cross reactivity
  - ε = symptoms not directly affecting the immune system

Pilcher WJ (Ed) *Drug Hypersensitivity* 2007, pg. 151-165

Biologics

- Reactions occur in 3-5% of patients treated with chimeric therapeutic monoclonal antibodies (TmAb's), 5-10% of patients treated with Rituximab.
- Reactions have been documented anywhere from the 1st through at least the 11th exposure.
- Can be immediate (minutes), delayed (> 6 hours), or very delayed (3-12 days)

Biologics

- Surfactants such as polysorbate 20 and polysorbate 80 that solubilize and stabilize proteins drugs can activate mast cells in an IgE-independent manner.

Biologics

- Cytokine release reactions (fever, rigors)
  - *via* antibody dependent cell mediated cytotoxicity (NK cells, Macrophages)
  - *via* target cell activation (T cells, B cells?)
  - *via* target cell destruction (T cells, B cells, other tumour cells) and the response to the cell debris ≈ tumour lysis syndrome

Biologics

- Adaptive immune responses to the agent
  - Drug specific IgE (presumably leading to leading IgE-dependent mast cell activation) has been documented to Basiliximab (chimeric anti-IL-2R TmAb) but seems to be rare.
  - IgG anti-drug, with FcγR mediated activation, complement activation, or both.

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