Virtually all chemotherapeutic agents have the potential to initiate infusion reactions.

Oncologic patients have higher survival rates → more re-exposure to the same chemotherapy agents due to recurrence of the disease.

Severe Hypersensitivity reactions (HSR) can lead to the suspension of first line treatments.

**MAIN TOPICS**

- Allergic reactions
- Hypersensitivity reactions
- Standard infusion reactions

**DIAGNOSIS**

- **Clinical evaluation**
  - Description of the reaction
  - Physical examination

- **In vivo evaluation**
  - Skin testing

- **In vitro evaluation**
  - Immediate analysis (serum tryptase, liver function, circulating immune complexes...)
  - Further investigation (specific IgE)
CLINICAL EVALUATION

- Identification of the drug responsible for the reaction
- Other drugs infusing at the same time or immediately before
- To quantify previous infusions with the same drug with no HSR
- Allergic symptoms in previous infusions
- Drugs taken at home / over the counter
- Food ingestion before the infusion
- Evaluation of infectious symptoms

CLINICAL EVALUATION

- Cutaneous symptoms: flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)
- Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality (due to laryngeal edema), hypoxia
- Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), hypotension, hypotension and/or loss of consciousness
- Gastrointestinal symptoms: nausea, vomiting, abdominal cramping, and/or diarrhea
- Neuromuscular symptoms: sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, pelvic pain

PHYSICAL EXAM

- General appearance - State of consciousness
  - Temperature
  - Signs of respiratory distress / Oxygen saturation
  - Dysphonia
  - Chest tightness
- Arterial Pressure – Lookout for hypotension  Anaphylactic shock !!!
- Observation of the skin and mucosae
  - Oropharynx (Tongue/uvula edema)
  - Angioedema
  - Observation and characterization of skin lesions
- Pulmonary auscultation – exclude wheezing
URTICARIA

ANGIOEDEMA

PHYSICAL EXAM

CUTANEOUS LESIONS

DRUG-INDUCED

VIRAL

MACULOPAPULAR RASH

PHYSICAL EXAM

ERYPHEMA MULTIFORME

STEVENS-JOHNSON SYNDROME

TOXIC EPIDERMAL NECROLYSIS

BLISTERING LESIONS

PHYSICAL EXAM
SERUM MEDIATORS

- Serum tryptase
  - In immediate reactions
  - Evaluates mast cell degranulation
  - Blood should be withdrawn from 20 minutes to 2 hours after the reaction

- Complement / Circulating immune complexes
  - For the diagnosis of type III reactions

- Exclusion of other potential causes
  - Reactive C protein
  - Viral serologies
  - Eosinophilia / liver function tests

- Total IgE and specific IgE to platins

Adapted from:

HYPERSENSITIVITY REACTIONS - CLASSIFICATION

According to timing

- Immediate (< 1 hour)
- Accelerated (> 1 h; < 24h)
- Delayed (> 24h)

According to Severity

Adapted from:

PATIENT ASSESSMENT

Adapted from:
COLLABORATION WITH ONCOLOGY

- When a HSR occurs in Oncology Day Care Unit
  - Call the Allergist

**Delayed reaction**
- Suspend and substitute the chemotherapy agent
- Pre-medications with anti-histamine and/or corticosteroids

**Immediate reaction**
- Taxanes / others: Clinical evaluation, Risk assessment
- Platin/ Monoclonals: Clinical evaluation, Skin testing, Risk assessment

No desensitization? **Consider Desensitization**

MOST FREquent AGENTS INDUCING HSR

- **PLATINUM SALTS** (12-19%)
  - Cisplatin (5 to 20%)
  - Carboplatin (9% to 27%)
  - Oxaliplatin (12% to 25%)

- **TAXANES** (5-45%)
  - Paclitaxel
  - Docetaxel

- **PEGYLATED LIPOSOMAL DOXORUBICIN**

- **PODO PHYLLOTOXINS** - Etoposide and teniposide …

- **MONOCLONAL ANTIBODIES** - Trastuzumab
  - Rituximab
  - Cetuximab …


IMMEDIATE REACTIONS

<table>
<thead>
<tr>
<th>ALLERGIC HYPERSENSITIVITY</th>
<th>NON-ALLERGIC HYPERSENSITIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic mechanism identified</td>
<td>Immunologic mechanism unknown</td>
</tr>
</tbody>
</table>
| Most frequently type-I (IgE-mediated) | Hypothesis...
  - Direct mast cell activation and degranulation?
  - Complement activation? |
| Requires prior sensitization (usually more than 2 exposures) | Reactions on the 1º or 2º exposures |
| Positive skin testing | Skin testing persistently negative |
| Diverse clinical presentation | Clinical presentation similar to IgE-mediated reactions |

**PLATINS**

**TAXANES**
PLATINUM SALTS

❖ Prevent cell division by inhibiting DNA replication → good anti-tumor activity in several solid tumors

❖ RHS described in platinum refinery workers - identification of specific IgE to platinum salts


❖ CISPLATIN: first to be used in the 70s → Nephrototoxicity

❖ CARBOPLATIN: second-generation platinum salt
  - Better toxicity profile
  - Gynecologic malignancies

❖ OXALIPLATIN: third-generation platinum derivative
  - Metastatic colorectal cancer

PLATINUM SALTS

❖ Classic type I IgE-mediated allergic reactions

❖ Require repeated exposures before the onset of the hypersensitivity

❖ Frequent presentation:
  → Pruritus, urticaria, bronchospasm, facial swelling, and hypotension

❖ Less frequent presentation:
  → type II reactions (immune-mediated hemolytic anemia or thrombocytopenia)
  → type III reactions (delayed vasculitic urticaria)

SKIN TESTING

➢ Crucial for the diagnosis of HSR to platin (good predictive value), and to some monoclonal antibodies

➢ Dilutions are prepared at the Pharmacy on the day of skin testing

➢ Performed by Allergists, two to four weeks after a HSR occurs, and to evaluate cutaneous sensitization even in the absence of a HSR

SKIN TESTING

Skin prick test

Intradermal
SKIN TESTING

Non irritant concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prick Concentration</th>
<th>Intradermal Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>≥ 10 mg/ml (1:1)</td>
<td>&gt; 10 mg/ml (1:1)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>≥ 5 mg/ml (1:1)</td>
<td>&gt; 3 to 5 mg/ml</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>≥ 1 mg/ml (1:1)</td>
<td>&gt; 1 mg/ml</td>
</tr>
</tbody>
</table>

- Sensitization is far higher after 6 carboplatin infusions
  - < 1% when less than 5 infusions
  - 19.5-27.5% more than 6 infusions

- Skin testing reliably predicts the majority of anaphylactic reactions to platinum-type drugs.
SPECIFIC IgE TO PLATINS

- 24 patients from Lisbon and Boston (Crb=12; Ox=12)
- Female:9; Male:5 (Mean age 61) with immediate hypersensitivity reactions to carboplatin and oxaliplatin
- Skin testing with culprit drug in 22 patients:
  - Crb=12   10 mg/ml
  - Ox=10     5 mg/ml

sIgE (UniCAP; Phadia™-Sweden) was performed for both platins (cut-off of 0.10 kU/l)

RESULTS: carboplatin sensitized patients

<table>
<thead>
<tr>
<th>Pts</th>
<th>Gender/ Age</th>
<th>Drug</th>
<th>Reaction</th>
<th>Skin tests (mg/ml)</th>
<th>sIgE Crb (kU/l)</th>
<th>sIgE Ox (kU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/54</td>
<td>Ox</td>
<td>Generalized rash, facial flushing, dyspnea,</td>
<td>Ox: 5 TCP</td>
<td>1.06</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>F/62</td>
<td>Ox</td>
<td>Itchy palms, Erythema, dyspnea</td>
<td>Ox: 0.5 ID</td>
<td>1.79</td>
<td>0.08</td>
</tr>
<tr>
<td>3</td>
<td>M/68</td>
<td>Ox</td>
<td>Facial flushing and lip angioedema</td>
<td>Ox: 0.5 ID</td>
<td>0.31</td>
<td>0.08</td>
</tr>
<tr>
<td>4</td>
<td>M/62</td>
<td>Ox</td>
<td>Facial flushing, Erythema, bronchospasm and</td>
<td>Ox: 0.5 ID</td>
<td>8.9</td>
<td>4.9</td>
</tr>
<tr>
<td>5</td>
<td>F/57</td>
<td>Ox</td>
<td>Facial flushing, Erythema, bronchospasm and</td>
<td>Ox: 0.5 ID</td>
<td>&lt;0.10</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>F/51</td>
<td>Ox</td>
<td>Facial flushing, e g encephalitis</td>
<td>Ox: 0.5 ID</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>7</td>
<td>F/60</td>
<td>Ox</td>
<td>Itchy palms, redness, nausea, shortness of</td>
<td>Ox: 5 TCP</td>
<td>0.31</td>
<td>0.45</td>
</tr>
<tr>
<td>8</td>
<td>M/68</td>
<td>Ox</td>
<td>Erythema, abdominal pain, hypotension, tremors</td>
<td>Not done</td>
<td>0.71</td>
<td>0.61</td>
</tr>
<tr>
<td>9</td>
<td>M/62</td>
<td>Ox</td>
<td>Palmar erythema, facial flushing and generalized rash</td>
<td>Ox: 0.5 ID</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>10</td>
<td>F/68</td>
<td>Ox</td>
<td>Generalized rash and hypotension</td>
<td>Ox: 0.5 ID</td>
<td>0.38</td>
<td>0.61</td>
</tr>
<tr>
<td>11</td>
<td>M/62</td>
<td>Ox</td>
<td>Itchy palms, facial flushing and urticaria</td>
<td>Ox: 0.5 ID</td>
<td>0.59</td>
<td>0.61</td>
</tr>
</tbody>
</table>

RESULTS: oxaliplatin sensitized patients

<table>
<thead>
<tr>
<th>Pts</th>
<th>Gender/ Age</th>
<th>Drug</th>
<th>Reaction</th>
<th>Skin tests (mg/ml)</th>
<th>sIgE Crb (kU/l)</th>
<th>sIgE Ox (kU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/64</td>
<td>Crb</td>
<td>Generalized rash, facial flushing, dyspnea,</td>
<td>Crb: 1 ID</td>
<td>1.06</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>F/62</td>
<td>Crb</td>
<td>Itchy palms, Erythema, dyspnea</td>
<td>Crb: 1 ID</td>
<td>1.79</td>
<td>0.08</td>
</tr>
<tr>
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<td>Crb</td>
<td>Facial flushing and lip angioedema</td>
<td>Crb: 1 ID</td>
<td>0.31</td>
<td>0.08</td>
</tr>
<tr>
<td>4</td>
<td>M/62</td>
<td>Crb</td>
<td>Facial flushing, Erythema, bronchospasm and</td>
<td>Crb: 1 ID</td>
<td>8.9</td>
<td>4.9</td>
</tr>
<tr>
<td>5</td>
<td>F/57</td>
<td>Crb</td>
<td>Facial flushing, Erythema, bronchospasm and</td>
<td>Crb: 1 ID</td>
<td>&lt;0.10</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>F/51</td>
<td>Crb</td>
<td>Facial flushing, e.g. encephalitis</td>
<td>Crb: 1 ID</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>7</td>
<td>F/60</td>
<td>Crb</td>
<td>Itchy palms, redness, nausea, shortness of</td>
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<tr>
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<td>Crb</td>
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<td>0.61</td>
</tr>
<tr>
<td>9</td>
<td>M/62</td>
<td>Crb</td>
<td>Palmar erythema, facial flushing and generalized rash</td>
<td>Crb: 0.5 ID</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>10</td>
<td>F/68</td>
<td>Crb</td>
<td>Generalized rash and hypotension</td>
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<td>Crb</td>
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<td>0.61</td>
</tr>
<tr>
<td>12</td>
<td>M/64</td>
<td>Crb</td>
<td>Generalized rash</td>
<td>Crb: 0.5 ID</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
</tbody>
</table>

F - Female; M - Male; Crb. Carboplatin; SPT - skin prick test; ID: intradermal
The timing of carboplatin ST in relation to initial HSR is vital for risk stratification and subsequent desensitization.

Initial ST negative patients with a remote history of HSR are at high risk for conversion to ST positive and can develop more severe HSR.

**TAXANES**

- Anti-myotic activity
- Treatment of several solid malignancies (ovary, breast, testicle, bladder)
- 1 incidence of HSR before the 90’s ( > 40%)

Inclusion of pre-medication with H1 and H2 anti-histamines and systemic corticosteroid in oncology protocols

Incidence dropped to <10%

**Cross-reactivity?**

- Paclitaxel: Cremophor
- Docetaxel: Polysorbate 80
- Substitutions may lead to similar reactions...

**TAXANES**

- HSR usually occur on the 1st or 2nd infusions (85%)
- Mechanism still not identified
  - Direct Mast Cell Activation and degranulation?
  - Complement activation?

But...

Clinical presentation similar to IgE immediate reactions

- Facial flushing
- Chest discomfort/pain
- Back pain
- Tachycardia
- Erythematous rash
- Hypotension
- Pruritus/urticaria
- Facial swelling
- Pneumonitis
- Maculopapular rash
- Erythrodysesthesia plaque

- Skin testing persistently negative → NOT RECOMMENDED!

Clinical assessment and treatment similar to IgE immediate reactions
MONOCLONALS

➢ Their use in Oncology is rising
  ✓ Rituximab (lymphoma)
  ✓ Trastuzumab (Breast cancer)
  ✓ Cetuximab (metastatic colorectal cancer)

➢ Skin testing
  ✓ Prick → full strength
  ✓ Intradermal → up to 1:10 dilution

➢ Clinical presentation
  ✓ Similar to other chemotherapy agents


Their use in Oncology is rising

Rituximab (lymphoma)
Trastuzumab (Breast cancer)
Cetuximab (metastatic colorectal cancer)

Skin testing
Prick → full strength
Intradermal → up to 1:10 dilution

Clinical presentation
Similar to other chemotherapy agents

PATIENT SELECTION

Immediate reaction suggesting type I HSR
Skin testing:
  Moderate - Severe reaction?
  Squibit infusion +/- premedication

Desensitization
Avoid medication

DESENSITIZATION - Daily Practice: results

➢ Total of chemotherapy desensitizations → 440

➢ Total of chemotherapy agents → 106

➢ Total of patients → 103

Platins
Taxanes
Anthracyclines
Monoclonal Antibodies
Example of a 12-step standard desensitization protocol

DESENSITIZATION – Daily Practice: results

DESENSITIZATION – Treatment of the reactions

Complete emergency kit:
- Cardiac monitor
- Equipment for arterial pressure and oxygen saturation evaluation
- Equipment for oxygen supply

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Treatment of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine 1:1000</td>
<td>In case of anaphylactic shock</td>
</tr>
<tr>
<td>IV Methylprednisolone</td>
<td>In case of severe urticaria or angioedema</td>
</tr>
<tr>
<td>IV Cimetidine 2 mg</td>
<td>In case of ulcer</td>
</tr>
<tr>
<td>IV Ranitidine 50 mg</td>
<td>In case of acid reflux</td>
</tr>
<tr>
<td>Inhaled Salbutamol</td>
<td>In case of bronchospasm</td>
</tr>
</tbody>
</table>

* ND: not done
CHARACTERISTICS OF THE REACTIONS

46 REACTIONS (11.5%) - in 35 patients

- Mild → 32 (7.2%)
- Moderate → 10 (2.2%)
- Severe → 4 (0.9%)
- 394 (89.5%)

MODIFICATIONS AFTER A HSR

IMMEDIATELY AFTER THE HSR

- Hold infusion
- Treat according to the protocol
- Resume desensitization EXACTLY at the point it was held

ADAPTATIONS IN FURTHER INFUSIONS

- When there is only mild reaction, do not alter the protocol
- Premedicate with clemastine and methylprednisolone before the step at which the patient has reacted
- Add 1 or 2 additional steps
- In step 12, reduce the maximum rate to 75 or 60 ml/h
- Initiate with a 1/1000 dilution instead of 1/100 (16-step protocol)
- When recurrent HSR have occurred or when the initial reaction was moderate to severe, especially with platins
  - Premedicate with aspirin and montelukast

2 days prior to the desensitization


Figure 1: Evolution of severity of reactions before and after acetylsalicylic acid and montelukast pretreatment. Under the ASA and montelukast pretreatment, 60% of patients were able to tolerate further desensitizations, with a low-severity hypersensitivity reaction or no reaction in grade 2.4% = grade 0.5. (P < .001).
Clinical assessment and risk stratification of HRS is crucial
Skin testing may predict anaphylactic reactions to platinum-type drugs
Similar clinical approach can immediate reactions (IgE and non-IgE mediated)
Importance in selection of patients amenable for desensitized
Learn how to design and adapt a desensitization protocol
Some patients may need special premedication protocols

Desensitization procedures allow the reintroduction of chemotherapy agents in patients with previous HSR.
From our experience, the majority of patients (426 – 97%) tolerated the procedure with only mild or no HSR.