Prevention and handling of acute allergic and infusion reactions in oncology

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OVERVIEW

- mechanism and definition
  - immune-type hypersensitivity reaction (HSR)
  - symptoms of acute infusion reaction (AIR)
  - clinical significance of AIR

- chemotherapy

- monoclonal antibodies (mAb)

- management of AIR

- what to do after AIR occurred

*not covered: AIR to contrast agents, blood products*
Infusion-related Adverse Drug Reactions (ADR)

- **intolerance** (type A)
  - **predictable** ADR at normal doses due to the pharmacological activity of the drug

- **idiosynkrasie** (type B)
  - **unpredictable** ADR due to individual predisposition, e.g. enzyme defect

- **HSR/AIR**
  - “drug allergy” and “pseudo-allergy”
  - one of four immune-type reactions
  - “anaphylaxis” and “anaphylactoid”
Four Immune-type HSR (Gell&Coombes)

- type 1: IgE-mediated
- type 2: IgG-mediated cytotoxicity
- type 3: Immunocomplex-mediated
- type 4: T Cell-mediated, cytokines, complement
HSR: immediate/non-immediate

- definition by: European Network for Drug Allergy

I. immediate Reaction after <1 hour of exposure
   - urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, overt anaphylaxis

II. nonimmediate Reaction after >1 hour of exposure
   - cutaneous symptoms, maculopapular eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia
## Spectrum of acute HSR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No reaction</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Local reaction only&lt;br&gt;Transient flushing or rash&lt;br&gt;Drug fever (&lt;38°C) (&lt;100.4°F)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Flushing&lt;br&gt;Mild bronchospasm&lt;br&gt;Rash, urticaria, dyspnea&lt;br&gt;Drug fever (\geq38°C) (\geq100.4°F)</td>
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<tr>
<td>Grade 3</td>
<td>Moderate bronchospasm,&lt;br&gt;Severe local reaction (&gt;10\text{mm or lasting}&gt;24\text{hours})&lt;br&gt;Serum sickness&lt;br&gt;Allergy-related edema/angioedema&lt;br&gt;Hypotension</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Anaphylaxis</td>
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<tr>
<td>Grade 5</td>
<td>Death</td>
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</table>
Anaphylaxis/Anaphylactoid Reaction: Oncologic Emergency!

- anaphylaxis (HSR)
  - systemic, immediate, IgE-mediated

- anaphylactoid reaction (AIR)
  - unspecific degranulation of mast cells or basophils

- risk factors for HSR
  - repeated administration of the drug ("priming")
  - predisposition = atopy
  - history (or family history) of drug allergy

www.esmo2012.org
Clinical Significance of AIR

- every drug infusion may cause (severe) AIR
- skilled personnel mandatory
- adequate premedication mandatory

CHEMOTHERAPY
Platinum Salts: Oxaliplatin

- mild/severe HSR in <25/1% of cases\(^1\)
- after 7-8 cycles, minutes after the start of infusion
- type I (II) reaction \(^2\)
- use H1/H2 blockers, steroids, slow infusion rate\(^3\)
- consider desensitization if oxaliplatin fundamental
- differentiate between acute neurotoxicity and HSR

\(^1\) Polyzos et al, Oncoogy 2009;76(1): 36-41.
Carboplatin

- mild/severe HSR in 19/2% after 8 cycles \(^1\)
- minutes to days after the start of infusion
- type I (IV) reaction
- use H1/H2 blockers, steroids, slow infusion rate
- switch to cisplatin in severe case (75% success)\(^2\)
- skin tests reliable

Cisplatin

- lower incidence of mild (0.4%) and severe HSR (0.8%) \(^1\)
- minutes from the start of infusion
- usually after ≥6 treatment cycles
- type I (IV) reaction
- skin test not reliable
- consider desensitization if cisplatin fundamental \(^2\)


Taxanes

- AIR primarily due to the solvent “cremophor EL” (paclitaxel) and “polysorbate 80” (docetaxel, cabazitaxel)
- solvent-triggered histamine release (not IgE)
- 30%/ ≤4% of patients without/with premedication
- dose- and infusion-rate dependent
- “hits early”: first minutes of infusion, first 2 cycles
- disappears on rechallenge and premedication

1Ardavanis et al, Anti-Cancer Drugs 2004, 15:581–585
Taxanes: AIR

- Symptoms: dyspnea, hypotension, urticaria, erythematous rash, tongue swelling, dysphagia

- Differentiate between platinum & taxane AIR when given in combination!

- Rapid normalization after discontinuation of the drug
Taxanes: Prevention of AIR

- oral dexamethasone 20mg –12 / –6(2) hours
- i.v. H1 and H2 blocker –30min
- dexamethasone prevention over 3 days for docetaxel
- i.v. dexamethasone 10-20mg –30min also safe\(^1\)
- severe AIR @rechallenge: desensitization or nab-paclitaxel\(^2\)
- cross-reactivity in 90%\(^2\)

\(^1\) Bookman et al, Annals of Oncology 8: 611-614, 1997
\(^2\) Fader et al, Int J Gynecol Cancer 2009;19: 1281Y1283
\(^3\) Dizon et al, Gynecol Oncol 2005;100(1):149-51.
L-Asparaginase

- enzyme from E. coli or Erwinia chrysanthemi
- 40% risk of IgE-mediated HSR (severe in ≤10%)\(^1\)
- risk factors: iv. (im.) application, previous exposure to L-Asp.\(^2\)
- allergic patients have enzyme-neutralizing Ab’s \(^3\)
- after HSR occurred:
  - Switch to Erwinia Asparaginase\(^4\)
  - Switch to PEG-Asparaginase (polyethylene glycol)\(^5\)

\(^2\) Demoly, Toxicology 2005; 209(2):221-23.
Procarbazine

- HSR caused by type I, III or IV reaction
- HSR in 6 to 18% of patients
- Symptoms include fever, maculopapular rash, urticaria, toxic epidermal necrolysis
- Rechallenge after HSR usually not successful, even with steroid prophylaxis
- No rechallenge

Podophyllotoxins

- AIR primarily due to the solvent “cremophor EL” (teniposide) and “polysorbate 80” (i.v. etoposide)
- AIR to teniposide in 6–41% ¹
- AIR to etoposide less frequent than with teniposide
- Importance of adequate premedication and slow infusion
- High cross-reactivity ²

Intermediate potential for AIR

- **Anthracyclines**
  - usually mild cutaneous symptoms
  - HSR may be prevented by low infusion rates
  - desensitization to liposomal doxorubicin is an option \(^1\)

- **Methotrexate**
  - infrequent, but potentially severe HSR
  - acute pneumonitis after some days following MTX\(^2\)
  - very rare, acute liver failure\(^3\)

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MONOCLONAL ANTIBODIES (mAb)
Monoclonal Antibodies (mAb)

- **murine with –o– stem**
  - tositumomab, ibritumomab

- **chimera with –xi– stem**
  - cetuximab, rituximab

- **humanized with –zu– stem**
  - alemtuzumab, bevacizumab, trastuzumab, pertuzumab, gemtuzumab

- **human with –u– stem**
  - panitumumab, ipilimumab, denosumab
mAb

- chimeric mAb: >50% human
- humanized mAb: 90% human
- fully humanized mAb: 99% human
- prevalent and induced anti-mouse Ab
- anti-mouse Ab → cytokine release (less prevalent HSR)
- AIR: stop infusion, H1/H2 blockers, restart at slow rate
mAb: General Remarks

- most AIR mild
- 2 pathomechanisms:
  - allergic → IgE
  - non-allergic → cytokine-mediated
- severe reactions are IgE-mediated
  - Consider desensitization, avoidance
- rechallenge successful with non-allergic reactions
- paracetamol & H1-blocker usually recommended
  ... except bevacizumab, panitumumab
mAb

- NCI grading criteria for cytokine-release infusion reactions

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<tr>
<td>1</td>
<td>Mild reaction; infusion interruption or intervention not indicated</td>
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<tr>
<td>2</td>
<td>Infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, steroids, IV fluids)</td>
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<tr>
<td>3</td>
<td>Prolonged symptoms (not rapidly responsive to symptomatic medication and interruption of infusion); recurrence of symptoms following initial improvement</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; vasopressors and/or ventilatory support indicated</td>
</tr>
<tr>
<td>5</td>
<td>DEATH</td>
</tr>
</tbody>
</table>

1National Cancer Institute 2010.
mAb: Specific Compounds

- **rituximab**: AIR in 77% @ 1\textsuperscript{st} application (7% severe HSR) \(^1\)

- **trastuzumab**: AIR in 40% @ 1\textsuperscript{st} application \(^1\)
  
  ....lower with s.c.-trastuzumab

- **alemtuzumab**: given s.c. in a fractionated way to avoid AIR

- **cetuximab**: C-IgE in 0.6-21% of the U.S. population \(^2\)

- **bevacizumab&panitumumab**: no premedication necessary

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Rituximab: Tumor lysis-type Reaction

- lymphocytes >25G/L, high tumor load
- hypotension and bronchospasm in 10% of pts @1st exposure
- electrolyte abnormalities, renal dysfunction, high LDH
- tumor cell agglutination > cytokine release
- stop infusion, do not restart before careful diagnostics and Tx
- prophylaxis: inpatient 1st exposure, fractionated dosing (100mg), allopurinol, hydration, close monitoring

MANAGEMENT OF AIR/HSR
Preparation

- obtain baseline assessment and vital signs
- assess for risk factors (eg. previous treatment)
- educate patient about potential symptoms of AIR/HSR
- make sure emergency equipment is available
- confirm that patient took premedication
Treatment

- stop infusion
- give i.v. volume, keep systolic BP >90mmHg
- supine position (if no vomiting or dyspnea)
- severe: call emergency, epinephrine
- maintain airway, consider O₂
- monitor vital signs q2min until baseline is reached
- documentation
(suspected) Anaphylaxis: Treatment Algorithm

Infusion STOP and call for HELP

- legs-up position
- secure airways
- CPR if necessary

ALWAYS (except only cutaneous)

Epinephrine i/m anterolateral thigh
- Epipen® 0.3 or 0.5 ml epinephrine (1mg/ml)
- children <30kg: Epipen® 0.15 or 0.2 ml epinephrine (1mg/ml)

Oxygen (mask, 6 L/min)

Monitoring (BP/Pulse, sO₂, Peak flow)
- Volume (NaCl 0.9% 500ml in 30min)
- Antihistamine i/v (clemastine 2mg slowly)
- Corticosteroid i/v (methylprednisolone 80mg)

Dyspnea hypotension reduced conciousness

BP<90mmHg P>100/min

no yes no

Inhalation: 5mg salbutamol or 1mg epinephrine in 1ml NaCl 0.9%

2-6 h monitoring (perhaps o/n)
STRATEGIES AFTER AN AIR/HSR OCCURRED
Specific Compounds

- **platinum salts:**
  mild-moderate HSR: use H1/H2 blockers, steroids, slow infusion rate,
  severe HSR: desensitize, cautious cross-over

- **taxanes, podophyllotoxins:**
  intensify premedication, no substitution (except nab-paclitaxel)

- **L-Asparaginase:**
  switch to Erwinia/PEG-Asparaginase, intensify premedication, desensitize

- **procarbazine:**
  discontinue

- **mAb**
  intensify premedication, slow infusion rate
  cetuximab $\rightarrow$ panitumumab

\(^1\)Langerak et al., ClinColorectal Cancer, 2009;8(1): 49-54.
Drug Desensitization

- only with IgE-mediated HSR
- mast cell desensitization* > tolerant state
- reversible process
- presence of trained allergist and nursing staff

*receptor downregulation, exhaustion of mediators, enhanced metabolism or drug efflux
Drug Desensitization: Protocol

- **conventional:**
  - escalating i.d. doses (e.g. 1 → 3 → 10 → 30 → 100)
  - increasing i.v. infusion rate

- **drug-specific, simplified (e.g. paclitaxel)**
  
  - 20mg oral dexamethasone –36/ –12/ –2 hrs
  - i.v. dexamethasone, H1 and H2 blocker –30min
  - paclitaxel 2mg/100ml NaCl/30min → 10mg/100ml/30min
  - remaining full dose in 500ml NaCl/3hrs

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CONCLUSIONS

- differentiate between HSR, AIR, intolerance & idiosynkrasie

- intensify premedication in case of solvent/mAb-related AIR

- desensitize or substitute in case of severe IgE-mediated HSR
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