Guidelines for Management of Intravenous Systemic Anti-Cancer Therapy Related Hypersensitivity Reactions including Anaphylaxis

INTRODUCTION/PURPOSE OF THE GUIDELINES
1. This document outlines the processes involved and the procedures to be followed in the event of a hypersensitivity reaction to any systemic anti-cancer therapy, including standard chemotherapy drugs, monoclonal antibody drugs and targeted therapies.
2. Certain standard chemotherapy drugs and many monoclonal antibodies have a relatively high risk of hypersensitivity reactions, ranging from mild flushing through to anaphylaxis. Managed correctly, most of the reactions will be mild to moderate, although it is important that the possibility of anaphylaxis is considered and when it occurs, it is detected early and the full anaphylaxis pathway is initiated.
3. Certain chemotherapy regimens include pre medication with steroids and other drugs to reduce the risk of hypersensitivity reactions. It is the responsibility of the nurse administering such treatment regimens to ensure that the patient has fully complied with their pre-medication regimen.

SUMMARY
4. These guidelines are intended to help nurses identify patients having hypersensitivity reactions to systemic anticancer medications and to correctly treat and manage these potentially life threatening situations. Patients experiencing severe hypersensitivity reactions (anaphylaxis) will be managed under the according to the anaphylaxis algorithm included in this guideline. This will include the emergency administration of intramuscular adrenaline.
5. Patients experiencing a less acute hypersensitivity reaction should be managed according to these local guidelines, including when it is appropriate, to administer hydrocortisone and chlorphenamine. Any patient not responding to these guidelines must be escalated immediately to the anaphylaxis protocol.
6. In some circumstances it is appropriate to re challenge patients with the drug which caused the hypersensitivity again, with senior medical agreement. This should only occur in cases of mild hypersensitivity reactions (grade 1 and 2) and should not be attempted following a second hypersensitivity reaction.
7. DEFINITIONS:
   • Hypersensitivity refers to undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
• Allergy is a type of hypersensitivity reaction and is an immune reaction that occurs to a normally harmless substance. Allergic reactions can range from mild reactions, such as urticaria (hives), or rhinitis (runny nose), up to anaphylaxis and death.

• Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. This is characterised by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes.

8. Allergic reactions have been graded by the National Cancer Institute Common Toxicity Criteria for Table 1 Adverse Events v4 and are categorized as follows:

<table>
<thead>
<tr>
<th>NCI Common Toxicity Criteria (CTC) for Adverse Events v4.0;</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome (Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breadth; it is caused by the release of cytokines from the cells.)</td>
<td>Mild reaction; infusion interruption not indicated; intervention not indicated</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for &lt;=24 hrs</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td>Life-threatening consequences; pressor or ventilatory support indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Transient flushing or rash, drug fever &lt;38 degrees C (&lt;100.4 degrees F); intervention not indicated</td>
<td>Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for &lt;=24 hrs</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Symptomatic bronchospasm, with or without urticaria; Parenteral intervention indicated; allergy-related edema/angioedema; hypotension</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. SIGNS AND SYMPTOMS OF AN ALLERGIC REACTION

An allergic or hypersensitivity reaction can include some or all of the following signs and symptoms:

• Skin reactions, such as urticaria, local flare, facial flushing or angioedema (subcutaneous swelling)
• Rhinitis
• Pyrexia
• Rigors
• Tachycardia
• GI symptoms, such as nausea, cramps or diarrhoea (Lenz 2007)

10. Anaphylaxis is likely when all of the following 3 criteria are met:
• Sudden onset and rapid progression of symptoms
• Life-threatening Airway and/or Breathing and/or Circulation problems
  ▪ Airway problems: throat and tongue swelling, stridor, hoarseness
  ▪ Breathing problems: wheeze, increased respiratory rate, fatigue, confusion caused by hypoxia, cyanosis, SpO2 < 92%
  ▪ Circulation problems: hypotension, dizziness, loss of consciousness
• Skin and/or mucosal changes (flushing, urticaria, angioedema)

11. Skin or mucosal changes alone are not a sign of an anaphylactic reaction

12. Skin and mucosal changes can be subtle or absent in up to 20% of reactions (some patients can have only a decrease in blood pressure, i.e., a Circulation problem)

13. There can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence)

14. In most cases, prompt and appropriate action in response to initial hypersensitivity symptoms, as specified in these guidelines, will prevent an allergic reaction to an infusion developing into a full-blown anaphylactic reaction.

CAUSES OF ALLERGIC REACTIONS

15. General medicinal products particularly associated with immediate hypersensitivity reactions include blood components (or medications derived from blood, e.g. immunoglobulin), vaccines and hyposensitising (allergen) preparations, contrast media, antibiotics and antifungal drugs, aspirin and other Non-Steroidal Antiinflammatory Drugs (NSAIDs), heparin and other neuromuscular blocking drugs.

16. Certain systemic anti-cancer treatments are associated with a higher risk of allergic hypersensitivity reactions.

Table 2: Chemotherapy drugs with reports of immediate hypersensitivity reactions

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase</td>
<td>Docetaxel</td>
<td>Amsacrine</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Carboplatin</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Oxaliplatin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Pegylated Liposomal</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin (Caelyx)</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Gemcitabine</td>
<td>Etoposide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitomycin C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab</td>
</tr>
</tbody>
</table>

17. Systemic anti-cancer therapies that contain “foreign” protein have an increased risk of such reactions. This includes:
• Asparaginase
- Monoclonal antibody treatments, such as trastuzumab (Herceptin®), rituximab (Mabthera®), or cetuximab (Erbitux®)

18. Platinum based drugs also have a higher risk of hypersensitivity reactions, for example, cisplatin, carboplatin, and oxaliplatin. In the case of the platinum based drugs the reaction may not occur on first administration, but is more likely to occur with successive treatments (Lenz 2007).

19. In the case of oxaliplatin, it is important to distinguish the possibility of an allergic reaction from pharyngolaryngeal dysaesthesia, which can occur during and just after the infusion of oxaliplatin, especially where the patient drinks a cold drink, or goes outside, particularly in winter. It is reported that this occurs in around 1 – 2% of patients. It is characterised by subjective sensations of dysphagia or dyspnoea and feelings of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). In this case the reaction is not accompanied by other signs of allergic reaction, such as flushing, urticaria, or angioedema (swelling). Patients should be managed by stopping the infusion (if still running) and with oxygen and supportive measures, until the dysaesthesia subsides. The administration of hydrocortisone and chlorphenamine is not indicated. In future treatments prolongation of the infusion helps to reduce the incidence of this syndrome.

20. Taxane chemotherapy drugs are associated with allergic reactions – paclitaxel and docetaxel. Hypersensitivity reactions generally occur within a few minutes of the start of the infusion of the drug and are usually mild to moderate. The most frequently reported symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills. Severe reactions are characterised by hypotension and/or bronchospasm or generalised rash/erythaema. In the case of paclitaxel, macrogol glycerol ricinoleate (polyoxyl castor oil), a drug excipient, is thought to be responsible for the hypersensitivity reaction.

21. All patients undergoing taxane chemotherapy regimens have premedication as part of the regimen including steroids in order to reduce the chance of an acute hypersensitivity reaction (Markman et al 2000, Yamada et al 2001). It is the role of the nurse administering the chemotherapy treatment to ensure that all necessary premedication treatment has been taken by the patient or administered by the nurse prior to the chemotherapy. Additional use of hydrocortisone and chlorphenamine if the patient were to develop an infusion related reaction may not be appropriate in this situation and the reaction should be escalated immediately to the medical team concerned, or, if indicated, the anaphylaxis policy instituted.
# MANAGEMENT AND TREATMENT OF AN ALLERGIC REACTION

See also the algorithms in appendix 1 and 2 anaphylaxis protocol

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>If an allergic reaction is suspected</td>
<td>Stopping the drug immediately may be sufficient to avert a more serious reaction</td>
</tr>
<tr>
<td>immediately stop the drug</td>
<td></td>
</tr>
<tr>
<td>Call for immediate nursing assistance</td>
<td>Alert colleagues to potential emergency situation and to get help</td>
</tr>
<tr>
<td>Assess the patient following ABCD principles</td>
<td>Follow the principles of emergency assessment</td>
</tr>
<tr>
<td>Assess the patient with respect to the grade of sensitivity reaction</td>
<td>To determine next action</td>
</tr>
</tbody>
</table>

**Grade 4 (anaphylaxis)**
*eg Rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes*

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute the Anaphylaxis Protocol. See anaphylaxis algorithm</td>
<td>This is a medical emergency</td>
</tr>
<tr>
<td>Call the Crash Team.</td>
<td>To get full emergency care backup</td>
</tr>
<tr>
<td>Adrenaline should be administered as an emergency intervention</td>
<td>Early intervention with adrenaline may be lifesaving.</td>
</tr>
<tr>
<td>Continue to monitor patient as clinically indicated</td>
<td>To detect further clinical changes.</td>
</tr>
</tbody>
</table>

**Grade 3 hypersensitivity reactions**
*eg Symptomatic bronchospasm, allergy-related oedema/angioedema, hypotension*

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administered high flow oxygen (&gt; 10 litres/min)</td>
<td>First line drug in emergency situation</td>
</tr>
<tr>
<td>Urgently summon medical assistance</td>
<td>Unstable patient may quickly deteriorate further</td>
</tr>
<tr>
<td>If not available call the crash team</td>
<td>To detect further clinical changes</td>
</tr>
<tr>
<td>Continue to monitor patient as clinically indicated</td>
<td>Any deterioration in condition requires full institution of anaphylaxis protocol</td>
</tr>
<tr>
<td>Any signs of clinical deterioration institute the anaphylaxis policy and escalate to grade 4 (above)</td>
<td>Any deterioration in condition requires full institution of anaphylaxis protocol</td>
</tr>
</tbody>
</table>

**Grade 2 hypersensitivity reactions**
*eg Rash; flushing; urticaria; dyspnoea; drug fever 38°C*

<table>
<thead>
<tr>
<th>Action</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recline patient to a comfortable position, with legs elevated (If the patient has breathing problems, they may prefer to sit rather than lie down)</td>
<td>To prevent hypotension.</td>
</tr>
<tr>
<td>High flow oxygen (&gt; 10 litres/min) must be administered</td>
<td>First line drug in emergency situation</td>
</tr>
<tr>
<td>Give prescribed chlorphenamine 10mg intravenously over at least ONE minute (if not given in premedication). Use Hydrocortisone and Chlorphenamine.</td>
<td></td>
</tr>
</tbody>
</table>
Give prescribed hydrocortisone sodium succinate 100 mg by slow IV injection (if not given in premedication). Use Hydrocortisone and Chlorphenamine. | Hydrocortisone has an onset of action that is delayed for up to 4-6 hours. However, it may shorten or prevent a protracted reaction. |
---|---|
If experiencing reaction despite previous steroids and chlorphenamine (i.e. during premedication—not antiemetic dose) call medical team for urgent review of patient | Further administration of hydrocortisone and chlorphenamine is unlikely to be beneficial. |
Continue to undertake patient observations: blood pressure, pulse, respiratory rate, oxygen saturation and temperature. Repeat every 15 minutes or as frequently as clinically indicated. | To detect further clinical changes |
Reassure and give clear explanation to patient and carer if present | Patient and accompanying relatives are likely to be alarmed about events |
Call for medical support if patient’s symptoms and signs are deteriorating | |
**Grade 1 hypersensitivity reactions**
*eg Transient flushing or rash; drug fever <38°C*
Continue to undertake patient observations. | To assess for deterioration or resolution of symptoms |
Consider the use of Hydrocortisone and Chlorphenamine if not been given as part of the pre-medications. | Hydrocortisone has an onset of action that is delayed for up to 4-6 hours. However, it may shorten or prevent a protracted reaction. |
Inform and discuss reaction with the medical team responsible | To ensure team aware of reaction and establish further management |
**In All Cases**
Complete a Trust Incident Form (Datix form). | Unexpected complication of care |
Fully document the nature and grade of the reaction and the drug involved using Aria and the Health Care Record | Ensure all staff fully aware of the reaction |
Ensure patient is aware of the name of the drug causing the reaction | Ensure patient knows to tell clinical staff in future. |

**ADMINISTRATION OF HYDROCORTISONE AND CHLORPHENAMINE**

22. In regimens with a high risk of hypersensitivity reactions premedication regimens will usually include high dose steroids. In this situation the repetition of further steroid doses with or without chlorphenamine would be unlikely to have further benefit.

23. Hydrocortisone and chlorphenamine are prescription only medications and must be prescribed before administration. In the case of day care, it is common for doctors not to be immediately available in the case of a reaction. For this reason a Patient Group Direction (PGD) for the
administration of Hydrocortisone 100mg slow IV bolus and Chlorphenamine 10mg slow IV bolus should be developed, whereby nurses working in Day Care covered under the PGD can deliver these medications in a specific clinical situation.

RE-CHALLENGING WITH THE DRUG

24. Re-challenge with the drug associated with the reaction on the same day may be considered if the following criteria are met:
   - The decision to re-challenge is made by a consultant oncologist/haematologist or registrar ST3+ or above in agreement with nursing staff.
   - The initial reaction was Grade 1 or 2.
   - The patient has fully recovered and is haemodynamically stable.
   - The infusion is re-started slowly, with a gradual increase in infusion rate only if tolerated.
   - The re-challenge occurs during normal working hours to ensure adequate emergency cover is available if required.

25. Re-challenge with the drug associated with the reaction on a later date may be considered if the following criteria are met:
   - The decision to re-challenge is made by a consultant in agreement with nursing staff.
   - Steroid cover is prescribed. A suitable regimen will consist of 20mg Dexamethasone twice daily starting the day before treatment and continuing until the day after treatment.
   - The infusion is started slowly, with a gradual increase in infusion rate only if tolerated.
   - The re-challenge occurs during normal working hours to ensure adequate emergency cover is available if required.

26. Patients on Rituximab infusions frequently have mild reactions requiring a temporary stopping and slowing of infusion. In these cases it is possible to re-challenge patients using the “Long-infusion” method without the need for consultant level agreement (see Rituximab guidelines).

27. Patients who develop a reaction to carboplatin, paclitaxel or cisplatin can be re-challenged using an appropriate “Desensitisation” regimen (i.e. Markman et al 2004, Castells et al 2008).

28. Any patient who does not tolerate the re-challenge, must have no further attempt made to continue treatment using this drug, and alternative treatment options need to be considered. In such cases the relevant drug MUST be documented as an allergy in the Health Care Records.
REFERENCES:


UK Resuscitation Council (2008), Emergency Treatment of Anaphylactic Reactions, Guidelines for healthcare providers.

Patients on Day Care/Ward receiving systemic anticancer therapy and having hypersensitivity reactions

Grade I: Transient flushing or rash; drug fever <38°C

Grade II: Rash; flushing; urticaria; dyspnoea; drug fever, ≥38°C

Grade III: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension

Grade IV: Anaphylaxis

Stop administration of the Anti-cancer therapy. Seek immediate help. Administer O₂ if required.

1. Check if patient is allergic to chlorphenamine hydrocortisone or other excipients.
2. Check if patient has already received pre-med antihistamine or steroid.

If either answer NO

Administer hydrocortisone and chlorphenamine

If either answer YES

Consult medical team. If not available, consult crash team

Clinical signs deteriorating

Consult medical team (SpR or Consultant) about re-challenge the drug, either on the same day or at a later date.

Clinical signs deteriorating

Anaphylactic Protocol
See next page for resuscitation council guidelines
Anaphylactic reaction?

Airway, Breathing, Circulation, Disability, Exposure

Diagnosis - look for:
• Acute onset of illness
• Life-threatening Airway and/or Breathing and/or Circulation problems
• And usually skin changes

• Call for help
• Lie patient flat
• Raise patient’s legs

Adrenaline

When skills and equipment available:
• Establish airway
• High flow oxygen
• IV fluid challenge
• Chlorphenamine
• Hydrocortisone

Monitor:
• Pulse oximetry
• ECG
• Blood pressure

1 Life-threatening problems:
Airway: swelling, hoarseness, stridor
Breathing: rapid breathing, wheeze, fatigue, cyanosis, SpO₂ < 92%, confusion
Circulation: pale, clammy, low blood pressure, faintness, drowsy/coma

2 Adrenaline (give IM unless experienced with IV adrenaline)
IM doses of 1:1000 adrenaline (repeat after 5 min if no better)
• Adult: 500 micrograms IM (0.5 mL)
• Child more than 12 years: 500 micrograms IM (0.5 mL)
• Child 6-12 years: 300 micrograms IM (0.3 mL)
• Child less than 6 years: 150 micrograms IM (0.15 mL)

Adrenaline IV to be given only by experienced specialists
Titrated: Adults 50 micrograms, Children 1 microgram/kg

3 IV fluid challenge:
Adult: 500 – 1000 mL
Child: crystalloid 20 mL/kg
Stop IV colloid if this might be the cause of anaphylaxis

4 Chlorphenamine
(IM or slow IV)
Adult or child more than 12 years: 10 mg
Child 6 - 12 years: 5 mg
Child 6 months to 6 years: 2.5 mg
Child less than 6 months: 250 micrograms/kg

5 Hydrocortisone
(IM or slow IV)
200 mg
100 mg
50 mg
25 mg

Originally authored by: Matthew Johnson from a Barts Health Guideline, Updated and added to include paediatric and anaphylaxis guidance found in the former NLGN guideline by: Simon Jenkinson
Version 1
Re-reviewed January 2014
Review Date January 2016
Paediatric Anaphylaxis/ Allergy Algorithm

- Assess ABC
- High flow oxygen
- Remove allergen (eg, stinger from bee sting)
- monitor ECG and BP
- Call paediatric team

Mild/localised reaction (urticaria, flushing Angio-oedema (+ no A/B/C problems)

- Oral chlorphenamine (see cBNF for oral doses)
- Observe
- Reassess, treat further symptoms as appropriate

Airway signs
- Stridor
- Hoarse voice
- Throat/tongue swelling

Breathing signs
- Wheeze
- Tachypnoea
- O₂ sats <92% in air

i.m adrenaline
- N.saline bolus 20ml/kg iv
- chlorphenamine i.m/i.v
- hydrocortisone i.m/i.v

Cardiovascular signs:
- Hypotension
- Collapse
- Pallor
- Drowsy

If no response in 5 mins
1. Paediatric crash call
2. Rpt adrenaline im – can be repeated every 5 mins if sustained poor response. Consider ivi adrenaline in these cases.
3. Repeat N/saline bolus if clinically indicated
4. If predominantly ‘asthma’ symptoms give nebulised salbutamol/ipratropium and follow severe/life-threatening asthma algorithm as clinically indicated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Adrenaline i.m (IM doses of 1:1000)</th>
<th>Hydrocortisone (IM or slow IV)</th>
<th>Chlorphenamine (IM or slow IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 months</td>
<td>150mcg IM (0.15ml) or Epipen 0.15mg autoinjector</td>
<td>25mg</td>
<td>250mcg/kg</td>
</tr>
<tr>
<td>6 months-6 years</td>
<td>150mcg IM (0.15ml) or Epipen 0.15mg autoinjector</td>
<td>50mg</td>
<td>2.5mg</td>
</tr>
<tr>
<td>6-12 years</td>
<td>300mcg IM (0.3ml) or Epipen 0.3mg autoinjector</td>
<td>100mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Over 12 years</td>
<td>500mcg IM (0.5ml) OR iV adrenaline (0.3mg/kg in 50ml) infusion starts at 0.1mcg/kg/min</td>
<td>200mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

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