

## 1. Infusion Related Reactions

### 1.1 Executive Summary

Infusion related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by patients during the infusion of cytotoxic or monoclonal antibody therapy (uniphasic reaction) and/or within hours of an infusion (biphasic/delayed reaction). The reaction may be caused by the therapeutic agent, diluent or delivery vehicle.

- **Symptoms can include: flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, oedema, nausea and all types of rashes.**

**Anaphylaxis** is recognised as a severe, life threatening, generalised or systemic reaction. This is a medical emergency situation characterised by rapidly developing life threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

**Anaphylactoid** reactions differ from anaphylactic in that no previous exposure to an agent is necessary. Signs and symptoms are the same as for anaphylaxis and the two conditions are treated in the same manner.

The severity of allergic or infusion –related reactions can be graded according to **CTCAE version 4**:

Adverse Event	1	2	3	4	5
<b>Infusion related reaction</b>	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <24 hours	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterised by adverse reaction to the infusion of pharmacological or biological substances.					

Adverse Event	1	2	3	4	5
<b>Allergic reaction</b>	Transient flushing or rash, drug fever < 38° C. intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics); prophylactic medications indicated for < 24 hours	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterised by an adverse local or general response from exposure to an allergen					

Adverse Event	1	2	3	4	5
<b>Anaphylaxis</b>	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

Adverse Event	1	2	3	4	5
<b>Cytokine release syndrome</b>	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids): prophylactic medications indicated for <24 hours	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death

Definition: a disorder characterized by nausea, headache, tachycardia, hypotension, rash and SOB; it is caused by release of cytokines from cells.

*The following information is designed as a quick reference for nursing and medical staff to initially manage these reactions. More comprehensive information including management follows this summary.*

## 1.2 Taxanes - Paclitaxel and Docetaxel

- Mild to moderate reactions occur in 30-40% of patients receiving taxanes
- 75% of reactions occur on the first dose and within the first 10 minutes.
- Back pain, chest pain, flushing and breathlessness, with or without wheeze and anxiety.
- Symptoms resolve very quickly when the infusion is stopped.
- The infusion can almost always be restarted after mild-moderate reactions.
- Serious reactions occur in 1-2% of patients and usually with the first infusion but can occur later

### Mild to Moderate Reactions



- Stop infusion
- Follow the flowchart for **mild to moderate** reactions
- Initiate standing orders

### Serious Reactions (wheeze and dyspnea/hypoxia, hypotension, generalised urticaria)



- Stop infusion
- Follow the flowchart for **serious** reaction
- Initiate standing orders

## 1.3 Platins - Cisplatin, Carboplatin, Oxaliplatin

- **Carboplatin/Cisplatin** commonest on 8<sup>th</sup> and 14<sup>th</sup> dose, i.e. the 2<sup>nd</sup> cycle in the 2<sup>nd</sup> or 3<sup>rd</sup> courses. The more given the higher the risk, also the longer the treatment break the higher the risk.
- Symptoms include: diffuse erythroderma, rash/itch, urticaria, chills, rigours, dyspnoea, wheeze, hypo/hypertension, respiratory arrest.
- **Oxaliplatin** rarely first cycle but more commonly from cycle 5.

- Symptoms include: itching of the palms and soles of the feet, facial flushing, rash and erythema, abdominal pain.
- Oxaliplatin laryngopharyngeal dysesthesia (cold intolerance) is not a hypersensitivity reaction. See full guidelines for management

### Mild to Moderate Reactions



- Stop infusion
- Follow the flowchart for **mild to moderate** reactions
- Initiate standing orders

### Serious Reactions



- Stop infusion
- Follow the flowchart for **serious** reaction
- Initiate standing orders

## 1.4 Monoclonal antibodies – rituximab, trastuzumab, cetuximab, panitumumab

- Symptoms may include: fever, chills, rigors, urticaria, hypotension and hypertension with headache, wheeze, breathlessness, hypoxia, pulmonary infiltrates
- A serious reaction can occur in up to 5% of patients and generally within the first two hours of treatment, mortality is higher in patients with existing cardiac and respiratory disease
- Colloids should not be given to patients reacting to rituximab as these can aggravate cell agglutination

### Mild to Moderate Reactions



- Stop infusion
- Follow the flowchart for **mild to moderate** hypersensitivity reactions
- Initiate standing orders

### Serious Reactions



- Stop infusion
- Follow the flowchart for **serious** hypersensitivity reaction
- Initiate standing orders

## 2. Infusion Related Reactions

### 2.1 Statement

The following information is designed to educate medical and nursing staff about infusion related reactions to commonly used cytotoxic or monoclonal antibody therapy.

### 2.2 Scope

Medical and nursing staff within the Canterbury Regional Cancer and Haematology Service, CDHB

### 2.3 Associated Documents

- Individual drug protocols
- Flow chart for management of mild- moderate reactions
- Flow chart for management of serious reactions
- Re-challenge protocols

### 2.4 Definitions

**Hypersensitivity** refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction

#### Type I Hypersensitivity

This is the most common type of reaction with oncology drugs

Type I hypersensitivity is also known as **immediate** or **anaphylactic** hypersensitivity. The reaction may involve skin (urticaria and erythema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (diarrhea and vomiting). The reaction may cause a range of symptoms from minor inconvenience to death. The reaction may occur from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 - 12 hours, up to 72 hours after administration). <http://pathmicro.med.sc.edu/ghaffar/hyper00.htm>

### 2.5 General Statements

Reactions may be triggered by the therapeutic agent, the diluent or the delivery vehicle.

**NOTE: For management of any reactions please see the associated flowcharts and the information below.**

**An infusion reaction kit should be kept in all areas delivering risk agents.**

**NOTE: Any serious reaction should be discussed with the appropriate consultant prior to any further treatment.**

## Taxanes - PACLITAXEL AND DOCETAXEL<sup>1, 2, 3</sup>

### Mild and moderate reactions

- Occur in up to 40% of patients on Paclitaxel and 30% of patients on docetaxel.
- Over 75% of reactions occur on the first dose, and within the first 10 minutes.
- Paclitaxel reactions are usually uniform, with flushing, back pain, chest pain, hypertension, breathlessness (without wheeze or hypoxia), chills and anxiety most commonly seen.
- Docetaxel reactions are also usually mild, with dyspnea, hypotension, bronchospasm, urticaria and rash
- These symptoms usually occur within minutes of starting the infusion, and reverse rapidly on stopping it (within 5-10 minutes).
- This clinical pattern of mild to moderate reactions to taxanes is remarkably consistent compared with more variable reactions to other agents.
- Only a small minority of patients experience repeated reactions beyond the second infusion, and an extremely small number go on to develop more severe reactions<sup>1</sup>.

### Management of mild and moderate reactions

- *Infusion should be stopped.*
- *In most cases it is possible to treat with IV antihistamines and steroids, and start the infusion again about 20-30 minutes after stopping, provided all signs and symptoms have completely resolved*
- *It is not usually necessary to change the routine pre-medication for the following cycle.*
- *If a second reaction occurs on the following cycle, consideration should be given to desensitisation.<sup>2, 4</sup>*

### Serious reactions

- Occur in up to 1-2% of patients, usually on the first infusion, but not infrequently on the second; usually within the first 10 minutes of treatment.
- Respiratory symptoms (breathlessness and bronchospasm) occur in 80% of serious reactions, urticaria/flushing/rashes in 75%, hypotension in 40% and angioedema in 20%.

### Management of severe reactions

- *Stop infusion and follow serious reaction pathway*
- *Re-challenge is possible with a 12 step desensitisation program<sup>2, 9</sup>.*
- *Substitution of 1 taxane for another is not recommended due to 90% cross –reactivity between the taxanes.*

## Platins - CISPLATIN AND CARBOPLATIN<sup>1,5</sup>

### Mild and moderate reactions

- The incidence of carboplatin reactions rises as the number of cycles rises. The most common cycle for reaction is the second cycle of a 2<sup>nd</sup> or subsequent course. The risk of reaction rises with increased interval since last carboplatin. In one study the risk of reaction rose from 6% if the last treatment was within a year, to 25% if last treatment was between 12 and 24m ago, to 47% if last treatment was over 2 years ago.<sup>6</sup>
- The timing of the reaction also varies widely, only half will react within the first few minutes of the infusion, some patients may react up to 3 days after treatment.

- Symptoms can resolve slowly
- Symptoms can include itching of the palms and soles, facial flushing, rash and erythema.
- These may be innocuous, but occasionally herald a serious reaction occurring on the next cycle.
- There do not appear to be any factors enabling prediction of those patients who go on to serious reactions after a mild reaction in the preceding cycle.

#### **Management of mild and moderate reactions**

- *Infusion should be stopped if the reaction occurs during the infusion.*
- *Most mild reactions occur after the infusion, and can be treated by antihistamines if symptoms do not settle quickly.*
- *Rechallenge should only be attempted after mild reactions, and with pre-medication including steroids, chlorpheniramine, and ranitidine.*

#### **Serious reactions**

- Comprise 30-40% of carboplatin reaction.
- Reactions involve skin (facial swelling, erythroderma), GI tract (cramps, diarrhea), respiratory system (dyspnoea, bronchospasm, wheeze, chest pain, respiratory arrest), and cardiovascular system (angina, tachycardia, hyper or hypotension)

#### **Management of serious reactions**

- *Stop infusion and follow serious reaction pathway*
- *High rates of recurrence have been reported with carboplatin re-challenge without prolonged desensitisation (2 of 3 pts mod-severe reactions)<sup>1</sup>.*
- *Re-challenge with cisplatin with short desensitisation has been reported to be more successful than with carboplatin re-challenge.<sup>7,8,9</sup> but needs to be considered carefully, weighing up the risks and perceived clinical benefit.*
- *Rechallenge with carboplatin is possible with a 12 step protocol<sup>9</sup>*
- *Moderate to severe reactions can reappear in later doses, despite successful re-challenge, so continuing prophylaxis is essential<sup>5</sup>.*

## **OXALIPLATIN**

### **Mild and moderate reactions**

#### **1) Non-specific allergic reactions<sup>10,11</sup>**

- These occur in about 0.5 –10% of patients.
- These reactions include flushing, tachycardia, minor swelling of the face and hands, itching of the palms and soles, rash, fever, sweating and lacrimation. Abdominal and chest pain may also occur.
- Reactions usually occur within minutes of starting the infusion up to very shortly after the infusion, and may occur on any cycle, but rarely on the first cycle.

#### **Management of mild and moderate non specific allergic reactions**

- *Infusion should be stopped.*
- *Treat with antihistamines and ranitidine if symptoms do not settle quickly.*
- *Rechallenge with pre-medication including dexamethasone, chlorpheniramine, and ranitidine may be used. Dexamethasone PO, 12 and 6 hours prior to Oxaliplatin may also be considered<sup>12</sup>. Premedication as above is not always successful in preventing recurrence<sup>8,9</sup>*

#### **Serious reactions**

- Only occurs in 1% of patients usually in the first hour, or occasionally delayed 2 hours after infusion.

- These include flushing, angioedema, sweating chills, GI symptoms, chest pain, tachycardia, dyspnoea, wheeze, agitation, and more severe manifestations of the mild symptoms described above.
- Occur on average at 7<sup>th</sup> or 8<sup>th</sup> administration, 5-10 minutes into treatment.

#### **Management of serious reactions**

- *Stop infusion and follow serious reaction pathway*
- *Rechallenge is risky, and should only be considered in extreme circumstances where benefit outweighs risk.*<sup>9-10</sup>

#### **2) Laryngopharyngeal dysesthesia**

- This occurs in all patients, and is not a hypersensitivity/allergic reaction.
- This presents as a sensation of respiratory distress or choking without any objective evidence of respiratory distress. This may be induced or exacerbated by exposure to cold.
- Patients should not receive cold drinks or ice chips day one of each cycle, and should avoid cold air.

#### **Management of laryngopharyngeal dysesthesia**

- *Infusion should be stopped.*
- *Assess oxygen saturation via pulse oximetry, and auscultate the chest. If there are no abnormal findings, then observe and reassure until episode resolves. An anxiolytic benzodiazepine may be considered.*
- *Once resolved, continue infusion at 1/3 the rate.*

<b>Monoclonal Antibodies -TRASTUZUMAB</b> <sup>13,14</sup>
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#### **Mild and moderate reactions**

- Fever, chills and rigors are common.
- Headaches, cough, dizziness (without hypotension) and hypertension are also seen.

#### **Management of mild and moderate reactions**

- *Infusion should be stopped.*
- *Appropriate medications should be administered (e.g. antihistamines, paracetamol if symptoms do not settle quickly)*

#### **Serious reactions**

- Occur in 0.3% of patients, usually on the first infusion, usually within the first 2 hours of treatment
- Respiratory symptoms (breathlessness, wheeze) are the most common symptom (66%), rigors in 30%, hypotension is seen in 14%, and rash in 8% of reactions.
- Mortality of serious reactions is 12% (i.e. total mortality is 0.04%).
- Mortality is seen almost exclusively in patients with pre-existing severe respiratory disease (Note this should therefore be a contraindication to treatment with Herceptin).
- About 1/3 of pts are able to be re-challenged successfully

#### **Management of serious reactions**

- *Stop infusion and follow serious reaction pathway*
- *Successful rechallenge with de-sensitisation has been described*<sup>15</sup>

## RITUXIMAB<sup>16</sup>

### Mild and moderate reactions

- The administration protocol is designed to minimize reactions and should be followed carefully.
- Note the special precautions in administration schedule for patients with circulating blasts.
- Fever, chills, rigors and urticaria are most commonly seen. Headaches, pain at disease sites, vomiting, myalgias, dizziness, rash and rhinorrhea are less common.

### Management of mild and moderate reactions

- *Infusion should be stopped.*
- *Symptoms are usually reversible on stopping.*
- *Treat with antihistamines; steroids and paracetamol +/- bronchodilators and IV saline if necessary (DO NOT GIVE COLLOIDS, as these may aggravate cell agglutination).*
- *Wait until complete resolution before resuming infusion at 50% rate reduction.*

### Serious reactions

- Occur in up to 10% of patients, usually within the first 2 hours of the start of the infusion.
- Respiratory symptoms (wheeze, breathlessness, hypoxia and pulmonary infiltrates on CXR) are commonest. Urticaria, angioedema, hypotension, myocardial infarction and shock are also seen.
- The respiratory syndrome may initially improve with treatment, then deteriorate again, close monitoring is essential.
- Fatalities occur in 0.04%, usually within the first 24 hours. Mortality is especially high in patients with pre-existing cardiac or pulmonary disease, and high numbers of circulating malignant cells.

### Management of serious reactions

- *Stop infusion and follow serious reaction pathway*
- *Desensitisation is possible following a 3 hour protocol<sup>9).17</sup>*

## CETUXIMAB

### Mild and moderate reactions

- These occur in about 20% of patients and include chills, fever and dyspnoea.
- Reactions mostly occur on the first dose, but may occur with subsequent doses.

### Management of mild and moderate reactions

- *Infusion should be stopped.*
- *There are reports of successful continuation with antihistamine administration and slowing the infusion.*

### Serious reactions

- Occur in up to 3% of patients, usually within the first 2 hours of the start of the first infusion.
- These reactions are typical hypersensitivity with bronchospasm, stridor and hoarseness, hypotension and urticaria.

### Management of serious reactions

- *Stop infusion and follow serious reaction pathway*
- *Desensitisation has been described with a simplified 5 step protocol<sup>15</sup>*

## DOCUMENTATION



- Record event in detail in clinical notes/concerto/Mosaic
- Record event on chemotherapy prescription
- If reaction is a serious reaction complete an incident form
- For serious reactions or new agents consider completing a CARM report (see below)
- Email the consultant to alert them of reaction

Response from CARM when asked what to report (2012)

1. *We would expect to receive reports where you believe that a particular agent may reflect a safety risk for the patient such that they shouldn't receive it again. Whilst I realise that these patients are often potentially terminally ill, not all are and that this would then facilitate the entry of a Medical Warning in the national system to alert other facilities in the event that they may attend there.*
2. *Any adverse event reports for newer agents are likely to be valuable for a national Centre such as CARM. This is on the basis that for many of the newer agents the clinical trials being small and efficacy orientated at best only identify the more significant adverse events and even then not the full spectrum of both serious and other adverse events. Therefore for any adverse events - even if you have seen them more regularly, it's likely that they would only be known in those centres that use them unless they are published or shared with National Centres such as CARM, other prescribers may not be as aware.*
3. *For the older agents any unusual events can be helpful in completing the picture for that agent.*

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<sup>1</sup> Zanotti K et al. Prevention and management of antineoplastic- induced hypersensitivity reactions. *Drug safety* 2001;24(10) 767-79

<sup>2</sup> Markman M et al. Paclitaxel associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic cancer center. *JCO* 2000, 18:102-5

<sup>3</sup> Pagani M. The complex clinical picture of presumably allergic side effects to cytostatic drugs: symptoms, pathomechanism, reexposure and desensitization. *Med Clin N Am* 2010 94:835-52

<sup>4</sup> Essayan et al., Successful parenteral desensitisation for paclitaxel. *J allergy Clin Immunol* 1996;97:42-6

<sup>5</sup> Markman M et al. Clinical features of hypersensitivity reactions to carboplatin. *JCO* 1999, 17:1141-5

<sup>6</sup> Schwartz J et al., Does the platinum-free interval predict the incidence or severity reactions to carboplatin? The experience from womens & infants hospital. *Proc ASCO* 2006. 24(18s):276s Abs 5082

<sup>7</sup> Ottaiano A et al. Safety of cisplatin after severe hypersensitivity reactions to carboplatin in patients with recurrent ovarian cancer. *Anticancer research* 2003, 23:3465-8

<sup>8</sup> Jones et al. Carboplatin hypersensitivity reactions: re-treatment with cisplatin desensitisation. *Gynecol Oncol* 2003 89:112-5

<sup>9</sup> Castells M et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80

<sup>10</sup> Lenz G et al. Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer drugs* 2003, 14(9): 731-3

<sup>11</sup> Brandi et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003, 89(3):477-81

<sup>12</sup> Thomas R et al., Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003, 97(9):2301-7

<sup>13</sup> Smith I. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. *Anti cancer drugs* 2001 12 (suppl 4):S3-10

<sup>14</sup> Cook-Bruns. Retrospective analysis of the safety of herceptin immunotherapy in metastatic breast cancer. *Oncology* 2001;61 (suppl2):58-66

<sup>15</sup> Hong et al. Allergy to monoclonal antibodies: cutting edge desensitisation methods for cutting edge therapies. *Expert Rev Clin Immunol* 2012 8(1):43-54

<sup>16</sup> Plosker et al., Rituximab. *Drugs* 2003; 63 (8) 803-43

<sup>17</sup> Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J. Allergy Clin. Immunol.* 124, 1259–1266 (2009).