



# Policy for the Management of Allergic Reactions and/or Hypersensitivity due to Chemotherapy and Monoclonal Antibodies

*“Quality and safety for every patient every time”*

## Document Control

Prepared By	Issue Date	Approved By	Review Date	Version	Contributors	Comments/ Amendment
Chemo Nurse Group	April 2011	Chemotherapy Group (NCG)	29.6.11	1.1	M. Vincent	Policy content approved pending amendments
	10.10.11	S.Williamson (Chair NCG)	1.10.12	1.2	C.Polwart	Agreed amendments included by Chairs Action
	1.11.12	S.Williamson (Chair NCG)	1.11.14	1.3	C.Polwart M Robertson	Review Date Updated
	3.11.15	S.Williamson (Chair NCG)	3.11.17	1.4	C.Polwart	Review Date Updated
	January 2018	S.Williamson (Chair NCG)	January 2021	1.5	C.Beck	Review Date Updated, rebranded to NCA and formatting changes, Added disclaimer and link to ESMO guidelines, new MABs, H2 antagonists, updated ALS & anaphylaxis appendices

## Contents

1. Aim .....	2
2. Scope .....	3
3. Objectives .....	3
4. Assessment .....	3
4.1 Symptoms .....	4
4.2 Preventative Measures .....	4
5. Management Guidance - Core Management Protocol .....	5
5.1 Specific Management of Cytotoxic Chemotherapy Hypersensitivity .....	6
5.2 Treatment of Mild Reactions (Adjunct to the core management protocol above) .....	6
5.3 Treatment of Moderate Reactions (Adjunct to the core management protocol above).....	6
5.4 Treatment of Severe Reactions (Adjunct to the core management protocol above) .....	7
5.5 Drug re-challenge procedure following a Moderate/Severe chemotherapy drug reaction .....	7
6. Management Guidance for Monoclonal Antibody Associated Hypersensitivity .....	9
Specific Drug Management.....	9
6.1 Trastuzumab (Herceptin® and / or Biosimilar Brands).....	9
6.2 Alemtuzumab (MabCampath®).....	10
6.3 Cetuximab (Erbix®).....	11
6.4 Rituximab (Mabthera® and / or Biosimilar Brands).....	12
6.5 Bevacizumab (Avastin®).....	13
6.6 Ofatumumab (Arzerra®).....	15
6.7 Obinutuzumab (Gazyvaro®) .....	16
7. Responsibilities .....	17
8. Monitoring and Review.....	17
9. Consultation and Ratification Process.....	17
10. Drug Specific References .....	18
Appendix 1 - Chemotherapy Agents commonly causing hypersensitivity reactions.....	20
Appendix 2 - Anaphylaxis .....	21
Appendix 3 - Cardiac Arrest.....	22
Appendix 4 - General principles pertaining to the management of hypersensitivity reactions in patients receiving intravenous Chemotherapy / Monoclonal Antibodies .....	23

### 1. Aim

This document outlines the process for the management of adult patients who experience a hypersensitivity reaction whilst receiving chemotherapy or monoclonal antibodies in organisations within the Network.

### Disclaimer

These guidelines do not give specific advice for all anticancer medicines that can cause infusion related reactions, only the most commonly used ones in Northern Cancer Alliance.

Readers are advised to read these guidelines in conjunction with local Trust policy and with the latest Guidance from European Society For Medical Oncology (ESMO)

**Reference:** S. Roselló, I. Blasco, L. García Fabregat, A. Cervantes, K. Jordan, Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines, Annals of Oncology, Volume 28, Issue suppl\_4, 1 July 2017, Pages iv100–iv118:

Available at [https://academic.oup.com/annonc/article/28/suppl\\_4/iv100/3958152](https://academic.oup.com/annonc/article/28/suppl_4/iv100/3958152) last accessed 05/01/2018

**N.B.** National guidance is available and should be followed when managing patients with treatment induced [anaphylaxis](#) (Appendix 2) and [cardiac arrest](#) (Appendix 3).

## 2. Scope

The term anaphylaxis is commonly used for an acute hypersensitivity reaction. It is typically mediated by immunoglobulin E (IgE) Type1 (immediate) immune reactions involve specific antigen, mast cells and basophils, as in drug reactions. When this reaction occurs in allergic disease the antigen is termed an allergen. Non-immunoglobulin mediated anaphylactoid reactions are similar, but do not depend upon hypersensitivity.

All drugs, including chemotherapy and monoclonal antibodies have the potential to cause allergic / anaphylactic reactions. With the increased use of combination chemotherapy and monoclonal antibodies, along with patients receiving a number of treatment regimens as part of the management of their cancer, there is a need for practitioners to be able to recognise and manage potentially fatal reactions to drugs.

For the purposes of this document adult patients are those individuals over the age of 18 years.

This Policy is designed to be complimentary to Trust Medicine Management/ Clinical Governance policies. In the event of any variation between advice given in this policy and in Trust policy, readers are advised to follow Trust policy and bring the matter to the Network Chemotherapy Group to discuss. Note the term Trust is used to describe any organisation within NECN where medicines are administered

## 3. Objectives

- To provide guidance to aid identification of the signs and symptoms associated with mild, moderate & severe hypersensitivity reactions.
- To provide guidance on the treatment and management of mild, moderate & severe hypersensitivity reactions.

## 4. Assessment

The key to successful management of anaphylaxis lies firstly in prevention and secondly in the accurate identification of the signs and symptoms of a hypersensitivity reaction. Reactions vary in severity and progress may be rapid, slow or unusually protracted or there may be a recurrence of symptoms (biphasic) after they initially seem to settle.

Hypersensitivity reactions can be mild, moderate or severe and are more likely to occur during the first or second infusion and often within minutes of commencing the drip. The degree of risk and type of reactions are variable from mild to life threatening

## 4.1 Symptoms

Hypersensitivity and anaphylaxis may present clinically with:

### Mild/Local symptoms including

Rhinitis

Pruritis (itch)

Conjunctivitis

Chill

Fever below 38°C

Headache

Light headedness / feeling faint

Nausea

Transient flushing or rash

Local florid / urticarial reaction spreading along the venous pathway of the IV access site

### Moderate symptoms include

Rhinitis

Pruritis

Conjunctivitis

Chill

Rigors

Fever above 38°C

Sense of impending doom

*Plus:*

Systemic urticaria (rash, flushing)

Mild bronchospasm / chest discomfort Cardiac dysfunction related to hypotension.

### Severe symptoms can include

Oedema/Angio-oedema (chest tightness, audible wheezing)

Bronchospasm (with or without urticaria)

Dyspnoea

Tachycardia

Hypotension

Abdominal pain

Vomiting

Diarrhoea

Skin colour changes i.e. flushed or pale

Loss of consciousness (but not cardiac arrest)

Cardiovascular collapse is a common manifestation especially in response to intravenous drugs and is caused by vasodilation and loss of plasma from the blood compartment.

**N.B.** Severe reactions can be fatal due to irreversible bronchospasm or laryngeal oedema.

## 4.2 Preventative Measures

Prompt interventions have the potential to reduce the severity of a hypersensitivity reaction and the following principles should be applied.

- Ensure all emergency equipment / medication is available within the treatment area.
- Consider nursing the patient on or near a bed or on a reclining chair.

- Prior to administration, advise patient / carer of the potential signs and symptoms of a hypersensitivity reaction and request that they report any symptoms immediately to a qualified nurse.
- Speak to the patient to establish medical history, existing allergies, atopic status (e.g. history of eczema, hay fever, asthma) and other medication (e.g. anti-hypertensives) the patient is taking.
- Record vital signs (temperature, pulse, respirations, blood pressure, oxygen saturation).
- Provide emergency buzzer.
- Review the patient's medical records to establish if there has been any previous history of hypersensitivity to the drug which is due to be administered. (only in exceptional circumstances, and with alternative arrangements [e.g. Intravenous and / or delayed oral premedication] may treatment proceed, and this must be with written instructions and the agreement of the patient's Consultant).
- There are some drugs with a greater propensity to induce a hypersensitive reaction and in these instances premedication is included and prescribed within the protocol e.g. oral dexamethasone and taxane (docetaxel, paclitaxel). Ensure any pre-medication is administered or has been taken as prescribed and in accordance with the treatment protocol. (If a patient has not correctly taken or received their pre-medication, as per their regimen protocol, their treatment should not be administered).
- Monitor the patient regularly (visually and verbally) throughout the intravenous infusion/bolus. Prior to a reaction, patients may report feeling odd or an urge to urinate or defecate, the patient should be evaluated by checking their blood pressure or pulse rate to check for further signs of hypersensitivity.
- Consider advising patients to withhold anti-hypertensives on the morning of treatments with significant risk of infusion related reaction if it is safe to do so.

## **5. Management Guidance - Core Management Protocol**

- Although the management of hypersensitivity reactions is dependent on the severity of the reaction, in all instances the following principles will apply:
- Stop the drug infusion / bolus.
- Maintain the patient's comfort, privacy and dignity and maintain open communication with the patient / family.
- Call for medical / nursing assistance.
- Record vital signs – Temperature, pulse, respirations, blood pressure, oxygen saturation to establish NEWS (National Early Warning Score) score.

Chemotherapy only - remove the intravenous infusion set if this is primed with the drug and replace with a new intravenous infusion set and begin administering prescribed sodium chloride 0.9% to maintain venous access.

**N.B.** Patients must be observed / monitored throughout hypersensitivity reactions as follows:

- Visually
- Communicatively (if possible)
- Recording of vital signs (every 15 – 30 minutes until the drug reaction subsides and the patient's condition stabilises, reducing to every 30 - 60 minutes until observations are within normal parameters and the patient is symptom free)

All drug reactions should be accurately recorded in the patient's nursing and medical notes and on the chemotherapy administration system or associated documentation.

## Cytotoxic Chemotherapy Hypersensitivity (Part 1)

### 5.1 Specific Management of Cytotoxic Chemotherapy Hypersensitivity

There are a number of cytotoxic drugs that have the potential to induce a hypersensitivity reaction (Appendix 1).

#### Premedication for previous reactors

- Patients who have previously displayed signs of a hypersensitivity reaction with a treatment drug should be prescribed intravenous antihistamine (Chlorphenamine 10mg) & corticosteroid (Hydrocortisone 100mg) and these should be administered prior to commencing treatment. **N.B.** Refer to re-challenge section when patients have had a moderate or severe reaction.

### 5.2 Treatment of Mild Reactions (Adjunct to the core management protocol above)

- Administer prescribed (or where local PGD exists via this) intravenous antihistamine (Chlorphenamine 10mg) & corticosteroid (Hydrocortisone 100mg) and observe / monitor the patient as detailed above.
- If the reaction has subsided, (in collaboration with colleagues) consider recommencing the infusion/bolus. If appropriate the infusion/bolus should be re-commenced slowly, e.g. at half speed.
- If the reaction recurs stop the infusion/bolus immediately and discuss the patient's management with senior medical staff – preferably the patient's consultant or ST3 or above.
- Observe / monitor the patient as detailed above.

### 5.3 Treatment of Moderate Reactions (Adjunct to the core management protocol above)

- Quickly move the patient into a private area and where appropriate / time permitting onto a bed
- Administer prescribed (or where local PGD exists via this) intravenous antihistamine (Chlorphenamine 10mg) & corticosteroid (Hydrocortisone 100mg) and observe / monitor the patient as detailed above.
- If oxygen saturation <95% and the patient has mild shortness of breath commence prescribed oxygen therapy (2 L/min via nasal cannula or 24% via face mask)
- Once the reaction has subsided and vital signs have been within normal limits for one hour and if the patient feels well enough to continue, liaise with medical staff regarding re-commencing the infusion / bolus.
- In the absence of a drug specific protocol for re-challenging a patient who has had a hypersensitivity reaction, start the infusion as outlined below.

Rate	Period of time
20ml/hr	15mins
40ml/hr	15mins
60ml/hr	15mins

If no reaction occurs the infusion rate may be increased to the correct rate of administration for that specific infusion

- The patient should be constantly visually and communicatively observed / monitored by a senior chemotherapy nurse or doctor for the first 45 minutes of the re-infusion to ensure that early signs/symptoms of hypersensitivity are recognised, and the infusion halted.

#### **5.4 Treatment of Severe Reactions** (Adjunct to the core management protocol above)

- Call for immediate nursing AND medical assistance
- Quickly move the patient into a private area and where appropriate / time permitting onto a bed
- If unconscious, lie the patient in a supine position.
- Administer prescribed intravenous drugs (or where local PGD exists via this)
  - Antihistamines – H1 & H2 (chlorphenamine 10mg IV & ranitidine 50mg slow IV) & corticosteroid (hydrocortisone 100mg IV).
  - Adrenaline (epinephrine) 0.5ml 1:1000 IM may be required for severe (i.e. anaphylactic) allergic reactions i.e. bronchospasm, angioedema and hypotension.
- If oxygen saturation <95% and the patient has mild shortness of breath commence prescribed oxygen therapy (2 L/min via nasal cannula or 24% via face mask)
  - Prescribed bronchodilators may be required e.g. nebulised Salbutamol 5mg
- If the patient experiences severe rigors, intravenous Pethidine 25mg may be required
- Ensure resuscitation equipment is brought to the patient's treatment area.

**N.B.** If the patient fails to respond to the above procedures or if their condition deteriorates manage the patient in accordance with guidance pertaining to anaphylactic shock.

- Maintain communication, with the family (and the patient once conscious).
- Once the reaction has subsided and vital signs have been within normal limits for one hour continue to record the patient's vital signs hourly for a further two hours, and then revert to 4hrly observations.
- Day case patients should in most instances be admitted overnight for observation.
- Patients who have had a severe reaction should only have a subsequent infusion/s of the drug responsible for the adverse reaction administered on the instruction of the patient's treating Consultant. The patient must be clearly identified to staff as being at risk of a further hypersensitivity reaction on re-challenge with the same drug and this must be clearly and specifically documented within the patients record/nursing record. If appropriate see section 5.1 regarding re-challenge for patients having a severe drug reaction to cytotoxic chemotherapy below.

**N.B.** The drug must not be administered within 2 to 3 days of the initial severe reaction.

#### **5.5 Drug re-challenge procedure following a Moderate/Severe chemotherapy drug reaction**

The decision to re-challenge should be made by the patient's consultant in discussion with the patient, senior nurses & pharmacists. The clinician may, in collaboration with the oncology pharmacist, evaluate the level of sensitivity using a patch test / test dose. The severity of the previous reaction must be considered and if the patient is to be re-challenged the patient must be re-listed for a mutually agreed appointment, usually a week after the initial reaction. The re-challenge should take place only when adequate medical and nursing staff are available within the treatment area.

- The patient should be allocated a cubicle.
- The patient must be allocated an experienced chemotherapy nurse administrator who will remain with the patient throughout the re-challenge/observation period.
- Oxygen therapy, resuscitation trolley and observational equipment (e.g. Dinamap) should be positioned within close proximity without causing any additional distress to the patient



## Monoclonal Antibody Hypersensitivity (Part 2)

### 6. Management Guidance for Monoclonal Antibody Associated Hypersensitivity

During the first infusion patients should be monitored for signs outlined in section 4.1 and they should also be observed for signs of severe cytokine release syndrome

- severe dyspnoea, often accompanied by bronchospasm and hypoxia
- fever, chills, rigors
- urticaria
- angioedema
- symptoms associated with tumour lysis syndrome (paraesthesia, weakness, tetany, anxiety, carpopedal spasm, bronchospasm, fatigue, nausea, vomiting, anorexia, metallic taste, restless legs, pericarditis, arthralgia and renal colic.

Although in most instances the management of hypersensitivity reactions would be in accordance with section 5 there is additional drug specific information which should be considered / applied as follows:

#### Specific Drug Management

##### **6.1 Trastuzumab (Herceptin<sup>®</sup> and / or Biosimilar Brands)**

Mild hypersensitivity reactions to Trastuzumab can occur in up to 40% of patients during a first infusion. To minimise the risk of a reaction the initial dose of Trastuzumab should be administered over 90 minutes and the patient should remain on the unit and be observed for at least six hours after the start of the first infusion and for two hours after the start of subsequent infusions for signs of fever or chills or other infusion related symptoms. Reactions usually occur within 2½ hours of commencing first infusion and mild reactions infrequently recur with future infusions. Severe reactions occur in a few patients. Patients with dyspnoea at rest due to pulmonary metastases or cardiac problems are more likely to experience severe reactions and should be treated with extreme caution.

##### **Mild – (First time or previous mild reaction only)**

If improves within 30-45 minutes

- increase to full speed

If the patient remains Symptomatic (e.g. headache / feeling slightly unwell or low grade pyrexia  $\leq 37.5$ )

- Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO).
- Once symptoms subside, re-start infusion at 50% of the initial infusion rate for 30 minutes and then increase to full speed if the patient remains asymptomatic.
- Signs of hypersensitivity – Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Consider re-starting infusion at 50% of the initial infusion rate for 30 minutes and then increase to full speed if the patient remains asymptomatic.
  - Previous moderate reaction – treat as per moderate management identified below but stop the infusion at the first sign of the patient experiencing an adverse reaction. ○

- o Previous severe reaction - Stop infusion, check pre-medication has been given. Continue only if symptoms resolve within 30-45 minutes as above.

### **Moderate**

- Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Provided the patient improves within 30 - 45 minutes re-start the infusion at 50% of the initial infusion rate and then increase to full speed if the patient remains asymptomatic. Patients should have an extended post infusion observation period of at least 2 hours following the completion of their infusion.
- If a patient experiences 2 or more moderate reactions they should receive a medical review prior to next treatment.

### **Severe**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. Do not restart infusion on that visit.
- **N.B.** A medical review (Consultant / ST3 or above) is mandatory following a severe reaction. Following a severe reaction, patients should be pre-medicated prior to subsequent infusions. On the first visit after a severe reaction, the patient should be monitored on the ward for 4 ½ hours after their infusion is completed. Providing subsequent administration / after care is uneventful post infusion observation can revert to the usual time period.

Patients should routinely be prescribed pre-medication if they experience a hypersensitivity reaction. Patients who have previously displayed signs of a mild hypersensitivity reaction should be prescribed Paracetamol (1G PO) and those having experienced moderate or severe hypersensitivity reactions should be prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Once a patient has received 3 cycles of treatment with pre-medication but without complications they should be re-challenged i.e. their next treatment should be administered without pre-medication but under strict supervision. Medication should be administered as prescribed if they experience any symptoms of hypersensitivity with any of their subsequent treatments. This does not apply to patients who have experienced a severe reaction and these individuals must have pre-medication prior to every subsequent cycle of treatment until their treatment is complete

### Accelerated Treatment.

If the initial loading dose was well tolerated, subsequent doses can be administered as a 30-minute infusion with 90 minutes post treatment observation.

### **6.2 Alemtuzumab (MabCampath®)**

The majority of these reactions are mild to moderate in severity. Acute infusion-related reactions usually occur during the first week of therapy and substantially decline thereafter. When used for bone marrow transplant conditioning, reactions tend to occur with the first treatment and within 4 hours of the start of the infusion. Additional specific symptoms associated with mild / moderate hypersensitivity include vomiting, hypotension, fatigue and diarrhoea.

The use of premedication and dose escalation (where appropriate) minimizes the risk of infusion reactions occurring. Before receiving Alemtuzumab, patients must receive the following premedication 30 minutes prior to the first infusion and before each dose escalation, and thereafter if clinically indicated. For transplant patients this premedication should be given prior to each infusion:

- Paracetamol PO 1g and Chlorphenamine IV 10mg

Oral or intravenous steroids may also be used for pre-medication (Hydrocortisone IV 100-200mg). If steroids are used it is recommended that they be phased out as soon as possible, either at the end of the first week or during the second week and should not be routinely used throughout treatment. If the patient is for transplantation steroids should routinely be given as pre-medication.

### **Mild / Moderate**

- Signs of hypersensitivity. Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Once symptoms subside restart infusion. It may be possible to decrease the rate of infusion and extend administration time to up to 8 hours. (However, in transplant patients the infusion will already be administered over 8 hours and it will not therefore be possible to reduce the rate)

### **Severe**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. Do not restart infusion on that visit.

**N.B.** A medical review is mandatory following a severe reaction. Following a severe reaction, patients should be pre-medicated prior to subsequent infusions

### **6.3 Cetuximab (Erbix<sup>®</sup>)**

Approximately 5% of patients will experience a hypersensitivity reaction during their infusion, of which about half are severe reactions. On completion of a Cetuximab infusion there must be at least a one-hour gap before commencing any chemotherapy. Severe reactions usually occur during the initial infusion and up to one hour after completing the infusion, although may occur after several hours. Patients should be warned about the possibility of late onset reactions. The patient's vital signs must be recorded prior to, during, on completion of and at least one hour after Cetuximab infusion.

Prior to receiving Cetuximab patients must receive the following premedication:

- Chlorphenamine IV 10mg
- Paracetamol PO 1g
- Ranitidine PO 150mg

Recommended rate of the first infusion is 120 minutes. Subsequent infusions may be given over 60 minutes, but the infusion rate should not exceed 10mg/ml.

### **Mild / Moderate**

- Signs of hypersensitivity. Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). If oxygen saturation <95% and the patient has mild shortness of breath commence prescribed oxygen therapy (2 L/min via nasal cannula or 24% via face mask). Prescribed bronchodilators may be required e.g. nebulised Salbutamol 5mg. Provided the patient improves within 30 - 45 minutes re-

start the infusion at 50% of the initial infusion rate and then increase to full speed if the patient remains asymptomatic. If the patient experiences a further reaction on the lower rate they should not receive any further Cetuximab. **(N.B.** The total infusion time for Cetuximab should not exceed 240 minutes - 2hrs for 200mg/m<sup>2</sup>, 4hrs for 400mg/m<sup>2</sup>)

### **Severe**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. Do not restart infusion on that visit.

**N.B.** A medical review is mandatory following a severe reaction. Following a severe reaction, patients should be pre-medicated prior to subsequent infusions.

### **6.4 Rituximab (Mabthera® and / or Biosimilar Brands)**

Mild to moderate hypersensitivity reactions to Rituximab occur in over 50% of patients and generally occur within one to two hours following the start of the first infusion. The risk of further reactions decreases with subsequent infusions. Severe hypersensitivity reactions occur in approximately 10% of patients and happen within minutes of starting the infusion.

Patients with a high tumour burden or patients with a high white cell count (>25 x10<sup>9</sup>/l), who may be at greater risk of severe cytokine release or tumour lysis syndrome should be treated with care. The decision to initiate or proceed with treatment in these high-risk situations must be made by the consultant responsible for the patient's care. Rituximab infusions for these patients are often delayed for example to day 5 instead of day 1 of a protocol or Rituximab may be omitted completely from Course 1. Where the decision to proceed is made patients require very close monitoring throughout the first infusion. Consideration may be given to the use of a reduced infusion rate for the first infusion or split dosing during first cycle (for instance, 100mg on day 1, with the remaining balance of the total dose on day 2) if the lymphocyte count is >25 x 10<sup>9</sup>/l.

A few small studies have demonstrated that it is possible on the second and subsequent infusions to administer Rituximab at a faster rate. Although this method is unlicensed many chemotherapy units have adopted the practice and have local protocols in use. A suggested rapid infusion protocol is outlined below.

The rapid infusion rate used is 20% (100ml) of the dose over 30 minutes (200ml/hour) followed by the remaining 80% over just 60 minutes (400ml/hour). Rapid infusion should only be considered for patients who have shown no signs of adverse reaction during previous infusions, and is contra-indicated in patients with high tumour bulk/burden or with high circulating lymphocyte counts.

Additional specific symptoms associated with mild / moderate hypersensitivity include throat irritation.

### **Additional / Specific preventative measures** (Adjunct to section 4.2)

Since hypotension may occur during Rituximab infusion, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the infusion. To minimise the risk of severe reactions occurring, one hour prior to the commencement of their infusion patients should be given the following prescribed premedication:

- Paracetamol 1g (oral)
- Chlorphenamine 4mg (oral) or 10mg (intravenously)

- Hydrocortisone 100mg (intravenously) unless the 1st dose of steroids within the chemotherapy treatment regimen have been taken before the Rituximab is commenced.

Patients must be observed / monitored every 15 minutes for the first hour and then hourly until completion of the intravenous infusion as follows:

- Visually, communicatively, recording vital signs as outlined above

N.B. For the first infusion patients who are at risk of tumour lysis will be prescribed Allopurinol 300mg in 2 or 3 divided doses, and some will require hospital admission for hydration and close monitoring. In some patients with biochemical evidence of incipient or established tumour lysis syndrome intravenous Rasburicase (0.2mg/kg for 5-7 days according to plasma uric acid concentration) may be more appropriate than Allopurinol. This decision will be made by senior medical staff responsible for the patient's care.

### **Mild / Moderate**

- Signs of hypersensitivity. Stop infusion and manage as per section 5, monitoring oxygen saturations continually. Administer prescribed medication as appropriate and dependent on the medication which has previously been administered / time frame e.g. intravenous antihistamine (Chlorphenamine 10mg), corticosteroid (Hydrocortisone 100mg) antiemetics (Ondansetron 8mg) and / or oral antipyretic (Paracetamol 1g). If the reaction has subsided recommence the infusion at half speed. If the reaction re-occurs stop the infusion/bolus immediately and discuss the patient's management with senior medical staff – preferably the patient's consultant or ST3 or above.

### **Severe Reactions**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. Administer prescribed medication as appropriate and dependent on the medication which has previously been administered / time frame e.g. intravenous antiemetics (Ondansetron 8mg) and / or oral antipyretic (Paracetamol 1g). In discussions with the patient's Consultant / ST3 or above, agree an action plan. The decision may be taken to abandon the infusion e.g. if patient has an underlying heart condition.

### **Drug re-challenge procedure following a Moderate/Severe drug reaction**

Discuss with the patient's Consultant / ST3 or above, the potential need to assess the patient for tumour lysis syndrome. The infusion should be commenced initially at half the previous rate until the dose reaches 400mg/hr.

### **6.5 Bevacizumab (Avastin®)**

Mild hypersensitivity reactions to Bevacizumab can occur in a number of patients during a first infusion. To minimise the risk of a reaction the initial dose of Bevacizumab should be administered over 90 minutes. Severe reactions occur in a small number of patients (<5%).

**Mild** – (First time or previous mild reaction only)

- Symptomatic (e.g. headache / feeling slightly unwell or low-grade pyrexia  $\leq 37.5^{\circ}\text{C}$ ) Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO). Once symptoms subside re-start infusion at 50% of the initial infusion rate for 30 minutes and then increase to full speed if the patient remains asymptomatic.

- Signs of hypersensitivity – Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Consider re-starting infusion at 50% of the initial infusion rate for 30 minutes. If symptoms improve within 30 - 45 minutes increase to full speed if the patient remains asymptomatic.
  - Previous moderate reaction – treat as per moderate management identified below but stop the infusion at the first sign of the patient experiencing an adverse reaction.
  - Previous severe reaction - Stop infusion, check pre-medication has been given. Continue only if symptoms resolve within 30 - 45 minutes as above.

### **Moderate**

- Stop infusion and manage as per section 5, administer prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Provided the patient improves within 30 - 45 minutes, re-start the infusion at 50% of the initial infusion rate and then increase to full speed if the patient remains asymptomatic. Patients should have an extended post infusion observation period of at least 2 hours following the completion of their infusion.
- If a patient experiences 2 or more moderate reactions they should receive a medical review prior to next treatment.

### **Severe**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. Do not restart infusion on that visit.
- **N.B.** A medical review (Consultant / ST3 or above) is mandatory following a severe reaction. Following a severe reaction, patients should be pre-medicated prior to subsequent infusions. On the first post severe reaction visit, the patient should be monitored within the ward for 4 ½ hours after their infusion is completed. Providing subsequent administration / after care is uneventful post infusion observation can revert to the usual time period.

Patients should routinely be prescribed pre-medication if they experience a hypersensitivity reaction. Patients who have previously displayed signs of a mild hypersensitivity reaction should be prescribed Paracetamol (1G PO) and those having experienced moderate or severe hypersensitivity reactions should be prescribed Paracetamol (1G PO), intravenous antihistamine (Chlorphenamine 10mg) and corticosteroid (Hydrocortisone 100mg). Once a patient has received 3 cycles of treatment with pre-medication but without complications they should be re-challenged i.e. their next treatment should be administered without premedication but under strict supervision. Medication should be administered as prescribed if they experience any symptoms of hypersensitivity with any of their subsequent treatments. This does not apply to patients who have experienced a severe reaction and these individuals must have pre-medication prior to every subsequent cycle of treatment until their treatment is complete

### Accelerated Treatment.

If the initial dose was well tolerated, subsequent doses can be administered as a 60-minute infusion, and then the next dose as a 30-minute infusion. Some institutions and trial protocols have administered bevacizumab as fast as 10minutes.

## **6.6 Ofatumumab (Arzerra®)**

61% of patients in pre-marketing trials experienced an infusion-related reaction, 7% experienced a severe (grade 3 or 4) infusion-related reaction. Reactions occur most frequently during the first cycle, and then are less likely for following cycles. Pre-medication should be given to all patients for cycle 1 of treatment.

Patients should be closely monitored during administration of ofatumumab for the onset of infusion-related reactions, including cytokine release syndrome, particularly during the first infusion.

### **Additional / Specific preventative measures**

All patients should receive pre-medication with

- Paracetamol 1000mg
- Chlorphenamine 10mg IV
- Hydrocortisone (200mg IV for first-line/relapsed treatment or 400mg IV for refractory disease).

On subsequent cycles, steroid doses can be reduced or omitted at discretion of the treating consultant if no severe reaction is experienced.

Infusion rate should be escalated in patients who do not experience infusion related reaction. Infusion rates and escalation depends on treatment number and indication. Consult product SPC for full details.

### **Mild / Moderate**

- Signs of hypersensitivity. Stop infusion and manage as per section 5, monitoring oxygen saturations continually. Administer prescribed medication as appropriate and dependent on the medication which has previously been administered / time frame e.g. intravenous antihistamine (Chlorphenamine 10mg), corticosteroid (Hydrocortisone 100mg), antiemetics (Ondansetron 8mg) and / or oral antipyretic (Paracetamol 1g). If the reaction has subsided, the infusion can be restarted at half of the infusion rate at the time of interruption once the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 ml/hour prior to interrupting due to an ADR, the infusion should be restarted at 12 ml/hour, the standard starting infusion rate.
- If the reaction re-occurs stop the infusion/bolus immediately and discuss the patient's management with senior medical staff – preferably the patient's consultant or ST3 or above.

### **Severe**

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. The infusion can be restarted at 12 ml/hour if considered appropriate after assessment by a consultant or ST3 or above when the patient's condition is stable. The infusion rate can continue to be increased according to standard procedures, to physician discretion and to patient tolerance (not to exceed increasing the rate every 30 minutes).

Ofatumumab should be permanently discontinued in patients who develop an anaphylactic reaction to the medicinal product.

## 6.7 Obinutuzumab (Gazyvaro<sup>®</sup>)

Patients with CLL are generally at a higher risk of an infusion related reaction than those treated for indolent NHL, 65% of CLL patients in pre-marketing trials experienced an infusion related reaction with their first dose, 20% of patients experience a severe (grade 3-4) reaction. Patients are at highest risk of reaction with their first cycle of obinutuzumab, with the risk substantially lower for the second infusion onwards.

Infusion rate should be escalated in patients who do not experience infusion related reaction. Infusion rates and escalation depends on treatment number and indication. Consult product SPC for full details.

### Additional / Specific preventative measures

In CLL, the first dose of obinutuzumab should be planned to be split over two days (100mg + 900mg) to mitigate the risk of a reaction. For the first 1000mg dose, all patients should be pre-treated with

- Dexamethasone 20mg IV
- Paracetamol 1000mg orally
- Chlorphenamine 10mg IV

From the second week onwards, the steroid can be omitted for patients who both have a lymphocyte count  $<25 \times 10^9/L$  and did not experience a grade 3 reaction with the previous dose. Chlorphenamine can be omitted if the patient experienced no infusion related reaction at all to the previous cycle.

Consider advising patients to withhold anti-hypertensives on the morning of treatments if it is safe to do so as this can reduce the severity of hypotension in the event of a reaction.

### Mild / Moderate

- Signs of hypersensitivity. Stop infusion and manage as per section 5, monitoring oxygen saturations continually. Administer prescribed medication as appropriate and dependent on the medication which has previously been administered / time frame e.g. intravenous antihistamine (Chlorphenamine 10mg), corticosteroid (Hydrocortisone 100mg), antiemetics (Ondansetron 8mg) and / or oral antipyretic (Paracetamol 1g). If the reaction has subsided, the infusion can be restarted at a reduced infusion rate (e.g. half of the rate at the time of interruption) once the patient's condition is stable. Infusion rate escalation can resume at the usual increments and rates as appropriate to the usual schedule.
- If the reaction re-occurs stop the infusion/bolus immediately and discuss the patient's management with senior medical staff – preferably the patient's consultant or ST3 or above.

### Severe

- Stop infusion with supportive care as indicated within organisation procedures and section 5.4 above. On recovery, the infusion can be restarted at a reduced infusion rate less than half of the rate at the time of interruption. If the patient does not experience any further infusion related reactions, rate escalation can resume as appropriate for the treatment.

Patients should discontinue treatment if they experience a life-threatening infusion related reaction or after two occasions of a grade 3 (prolonged/recurrent) reaction (either when resuming or on a subsequent re-challenge).

## **7. Responsibilities**

General staff responsibilities:

- Within induction programmes, qualified oncology nurses should be made aware of the signs and symptoms of hypersensitivity / anaphylaxis in order to facilitate early detection and treatment and therefore improve outcomes.
- Chemotherapy nurse administrators undertake specific competency assessments which include the identification and evidence based management of anaphylaxis / hypersensitivity within their cytotoxic chemotherapy training and this is evaluated annually.
- Hypersensitivity reactions must be managed in accordance with these guidelines and organisational policies.

Line manager responsibilities:

- Ensure the staff involved in the management of hypersensitivity reactions have received the appropriate education and have shown themselves to be competent in the roles they perform.
- Ensure the appropriate resources are available to safely manage patients in accordance with local / national guidelines.

## **8. Monitoring and Review**

The effectiveness of this guidance will be monitored via the North of England Cancer Network.

## **9. Consultation and Ratification Process**

This guidance has been developed in consultation with the medical, nursing and pharmaceutical staff from the Cancer network. Acknowledgements:-

A Lennard, M Vincent, B Aniolkowski, S Campbell, E Reay and P Gamble Newcastle Hospitals NHS FT. The document will be reviewed in 3 years or as determined by available evidence / modifications in practice.

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## **Appendix 1 - Chemotherapy Agents commonly causing hypersensitivity reactions**

### **Carboplatin**

Carboplatin hypersensitivity reactions have been observed more frequently due to the increased use of the drug as a single agent or in combination. Patients treated with multiple course of Carboplatin are more likely to experience a hypersensitivity reaction, with the incidence of reactions increasing to 27% in patients who have received greater than seven cycles of Carboplatin, with more than 50% of patients experiencing a moderate to severe reaction. Reactions may occur within several minutes of the infusion commencing or delayed reactions may occur hours or days after the infusion.

Additional specific symptoms associated with mild / moderate hypersensitivity include itchy hands.

### **Liposomal Doxorubicin**

Infusion related reactions can be life-threatening and are characterised by allergic-like or anaphylactoid like reactions. They generally occur during the first infusion. To minimise the risk of hypersensitivity reactions the initial infusion should be administered at a rate no greater than 1mg/minute. If no reaction is observed subsequent infusions may be administered over 60 minutes.

### **Docetaxel**

Hypersensitivity reactions to Docetaxel can be mild, moderate or severe and are more likely to occur during the first or second infusion often within minutes of commencing the infusion. To minimise the risk of a hypersensitivity reaction the patient should receive oral Dexamethasone pre-medication, as per regimen protocol.

### **Oxaliplatin**

Hypersensitivity reactions to Oxaliplatin may be of varying severity and usually occur after six or more cycles, very rarely resulting in full-blown anaphylaxis (approximately 0.5% of patients). A hypersensitivity reaction is more likely to be seen when Oxaliplatin is used in combination with 5FU +/- Folinic Acid. Patients who have a history of allergic reaction to platinum compounds should be monitored closely as they are more likely to experience hypersensitivity reactions. Hypersensitivity reactions may sometimes be confused with a laryngeal dysphagia.

### **Paclitaxel**

Mild hypersensitivity reactions to Paclitaxel are common and severe reactions are very uncommon. Reactions occur in less than 1% of patients who have received premedication. To minimise the risk of severe reactions occurring patients must receive either:

- Dexamethasone 20mg IV – 45 minutes before Paclitaxel infusion **Or**  
Dexamethasone 20mg orally 12midnight & 6am prior to chemotherapy
- Chlorphenamine 10mg IV – 30 minutes before Paclitaxel infusion
- Ranitidine 50mg as an IV infusion over 15/30 minutes in Sodium Chloride 100ml before Paclitaxel infusion

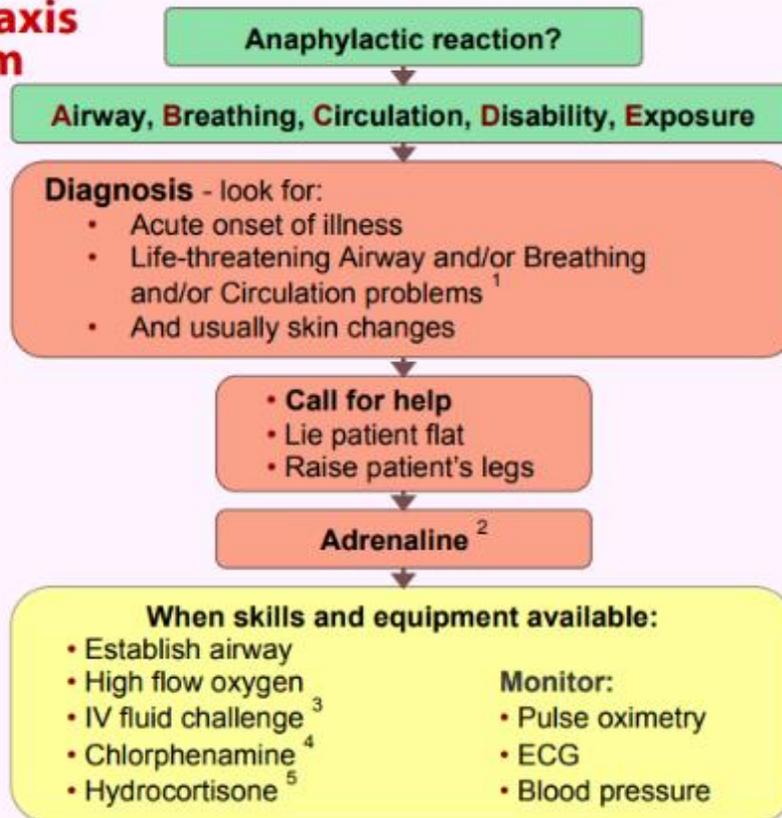
Additional specific symptoms associated with mild / moderate hypersensitivity include chest and severe back pain.

## Appendix 2 - Anaphylaxis



Resuscitation Council (UK)

### Anaphylaxis algorithm



#### 1 Life-threatening problems:

**Airway:** swelling, hoarseness, stridor  
**Breathing:** rapid breathing, wheeze, fatigue, cyanosis, SpO<sub>2</sub> < 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**  
 Titrate: 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

March 2008

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Issue Date: January 2018

Page 21 of 23

Expiry Date: January 2021

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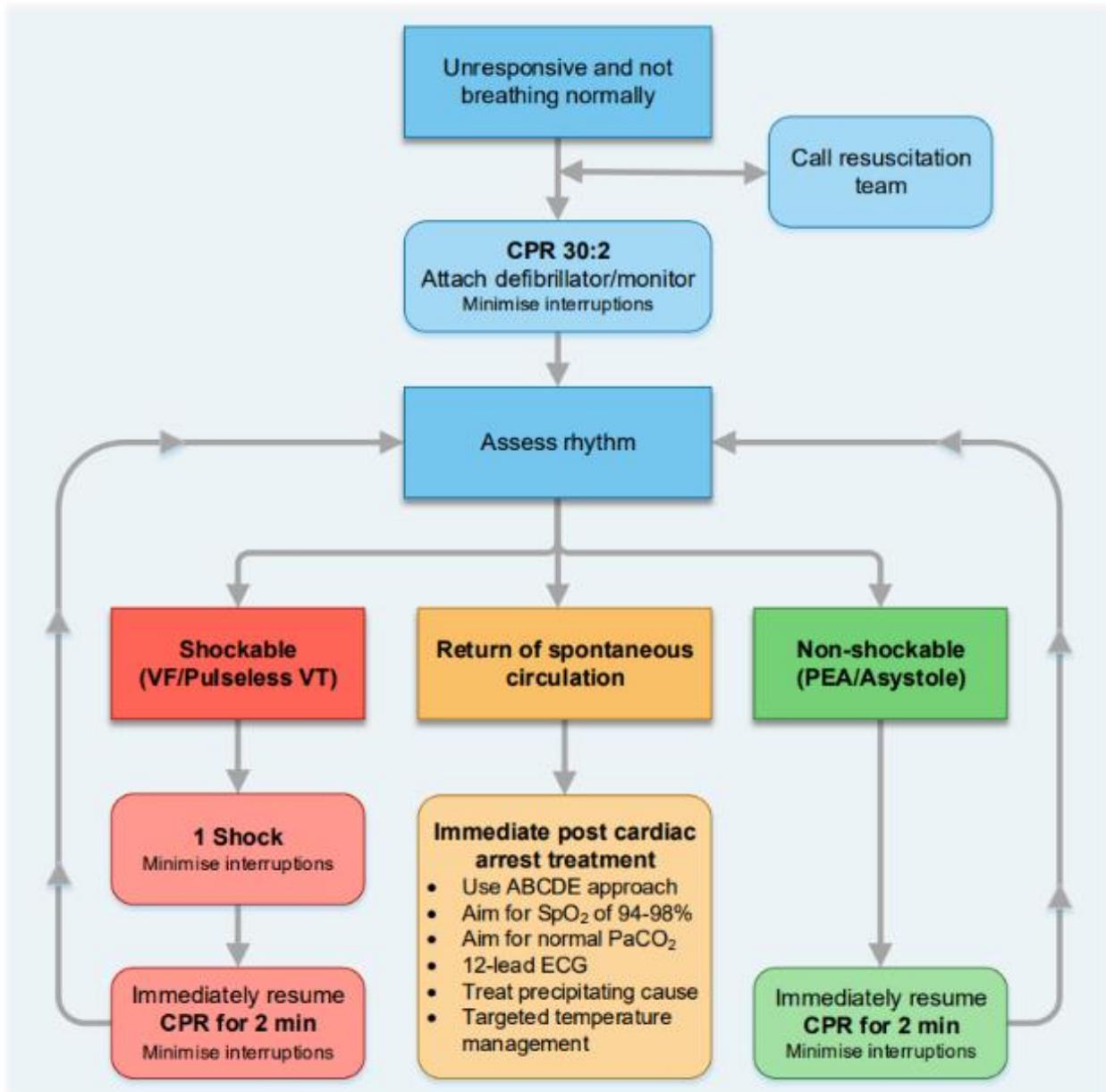
## Appendix 3 - Cardiac Arrest



Resuscitation Council (UK)



Adult Advanced Life Support



- During CPR**
- Ensure high quality chest compressions
  - Minimise interruptions to compressions
  - Give oxygen
  - Use waveform capnography
  - Continuous compressions when advanced airway in place
  - Vascular access (intravenous or intraosseous)
  - Give adrenaline every 3-5 min
  - Give amiodarone after 3 shocks

- Treat Reversible Causes**
- Hypoxia
  - Hypovolaemia
  - Hypo-/hyperkalaemia/metabolic
  - Hypothermia
  - Thrombosis - coronary or pulmonary
  - Tension pneumothorax
  - Tamponade – cardiac
  - Toxins

- Consider**
- Ultrasound imaging
  - Mechanical chest compressions to facilitate transfer/treatment
  - Coronary angiography and percutaneous coronary intervention
  - Extracorporeal CPR

<https://www.resus.org.uk/resuscitation-guidelines/>

## Appendix 4 - General principles pertaining to the management of hypersensitivity reactions in patients receiving intravenous Chemotherapy / Monoclonal Antibodies

