GUIDELINE FOR THE MANAGEMENT OF IMMUNE-RELATED ADVERSE REACTIONS FOLLOWING IMMUNOTHERAPY TREATMENT

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

This guideline refers to the management of immunotherapy induced adverse reactions. It encompasses the pathway of care to follow when a patient over the age of 16 who has received immunotherapy in adult services presents to Worcestershire Acute Hospitals NHS Trust.

This policy refers to all patients over the age of 16 who have received immunotherapy in adult services within the last 12 months presenting to Worcestershire Acute Hospitals NHS Trust.

This guideline is for use by the following staff groups:

This guideline is for utilisation by trained medical and nursing staff. Educational updates will be provided for medical and nursing staff.

Lead Clinician(s)

Helen Grist	Immunotherapy CNS
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Mrs S Cook	Lead Pharmacist
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Guideline approved by Accountable Director on: 15th September 2017

Review Date: 9th November 2020

This is the most current document and is to be used until a revised version is available

Key Amendments made to this document:

Date	Amendment	By
	Guideline approved by Clinical Effectiveness Committee	
9th October 2019	09/10/2019- Document extended for 6 months whilst document is taken through consultants meeting and reviewed	Helen Grist/Lisa Rowberry
May 2020	Document extended for 6 months during COVID-19	

Worcestershire Acute Hospitals NHS Trust

Contents

Section:-

Guideline For The Management of Immune-Related Adverse Reactions Following Immunotherapy Treatment

1. INTRODUCTION

This policy refers to the management of immunotherapy induced adverse reactions. It encompasses the pathway of care to follow when a patient over the age of 16 who has received immunotherapy in adult services presents to Worcestershire Acute Hospitals NHS Trust.

2. DEFINITIONS

Immunotherapy agents are a relatively new class of anti-cancer drugs which stimulate the body's immune system to fight cancer cells. The side effect profile for these agents is different from that of standard cytotoxic drugs, they can cause severe immune-related adverse reactions which can be fatal including serious immune-related endocrinopathies, thus it is important to recognise and address symptoms early.

The majority of immune-related reactions occur over the course of treatment, however, they can occur weeks to months after discontinuation of treatment.

3. PRE TREATMENT INVESTIGATIONS AND PATIENT EDUCATION

Prior to commencing treatment all patients must be informed of the potential side effects (Risk of adverse reactions) and what action to take should they experience these side effects. All patients must be given drug specific information and an immunotherapy alert card containing contact details for the acute oncology service. Patients should be advised to contact the hospital straight away if they have any of the following symptoms:

- Lung problems: breathing difficulties or cough
- Diarrhoea: watery or loose stools, mucous or blood in stool, stomach pains or cramps
- Liver problems: eye or skin yellowing, pain on right side of stomach
- Kidney problems: changes in volume of urine

- Gland problems: extreme tiredness, weight change, headache, visual disturbances
- Diabetes symptoms: excessive thirst, large volumes of urine, increased appetite with weight loss, feeling tired, drowsy, weak, depressed, irritable and generally unwell
- Skin problems: itching, rash, blisters, ulcers, peeling skin
- Eye problems: redness, pain, blurred vision
- Other: severe upper abdominal pain, nausea, vomiting, numbness, uncoordinated movements, paralysis, muscle weakness

Prior to initiation of treatment the following bloods should be taken as a baseline:

- FBC, LFT's, Renal profile, Glucose, Cortisol, TSH, LDH

These bloods should be repeated before each cycle.

If the patient is stable on treatment the frequency of the blood test may be reduced.

Patients should be reviewed prior to each of the first two cycles and then every other cycle. If the patient is stable on treatment the frequency of review may be reduced.

If the patient contacts the acute oncology service out of hours, the AOS nurse should complete the Immunotherapy 'Out of Hours Checklist' (Appendix 1) and follow the instructions on the checklist.

If the patient contacts the acute oncology service during normal working hours or presents at the accident and emergency department they should be assessed and managed as detailed in the 'Initial Management of Immune-related Adverse reactions' table below.

4. MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS INDUCED BY IMMUNOTHERAPY

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INITIAL MANAGEMENT of IMMUNE – RELATED ADVERSE REACTIONS

INFORM CONSULTANT ONCOLOGIST

On presentation, if no obvious infectious and / or disease-related aetiologies

DO NOT WAIT, TREAT AS:

Immune –Related Adverse Reaction or Endocrinopathy as tables below.

Follow link for CTC grading criteria:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Immune Related-Adverse Reactions

	Grade 2 or Above	Grade 3 or Above
Pneumonitis Cough, dyspnoea, hypoxia, radiographic changes eg. focal ground glass opacities	Initiate Corticosteroid:1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg and 5mg available)	
Colitis Watery, loose stools, blood or mucous in stool, abdo pain	Initiate Corticosteroid:1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size25mg and 5mg available)	
Hepatotoxicity Raised AST, ALT or total Bilirubin, right sided abdo pain, tiredness	If persistent initiate corticosteroid: 0.5 – 1mg/kg/day IV methylprednisolone **OR** 0.625 – 1.25 mg/kg/day oral prednisolone (round to nearest tablet size 25mg and 5mg available)	Initiate Corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg and 5mg available)
Nephrotoxicity Asymptomatic increase in creatinine, other abnormal renal function, decreased volume of urine	Initiate Corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg and 5mg available)	
Rash Itching, blisters, ulcers, peeling skin		Initiate Corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg and 5mg available)

Immune-Related Endocrinopathies

	Hormone replacement	Steroids
Symptomatic Hypothyroidism	Initiate thyroid hormone replacement as needed	Consider corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg or 5mg) If acute inflammation of the thyroid is suspected
Symptomatic Hyperthyroidism	Initiate carbimazole as needed	Consider corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg or 5mg) If acute inflammation of the thyroid is suspected
Symptomatic Grade 2 adrenal insufficiency	Initiate physiological corticosteroid replacement as needed	
Symptomatic Grade 2-3 Hypophysitis	Initiate hormone replacement as needed	Consider corticosteroid: 1 – 2 mg/kg/day IV methylprednisolone **OR** 1.25 – 2.5 mg/kg/day oral prednisolone (round to nearest tablet size 25mg or 5mg) If acute inflammation of the pituitary gland is suspected
Symptomatic Diabetes	Initiate insulin therapy as needed	

5. ONGOING MANAGEMENT

Treatment should be withheld for patients suffering any grade 2 or above toxicity. The ongoing management will be co-ordinated by the consultant oncologist in charge of the patients care.

6. CONTACT NUMBERS FOR ADVICE

Acute Oncology Service 24 hours a day, 7 days a week	01905 760158 / 30049
Acute Oncology Nurse Practitioners (Mon-Fri 0900-1700)	Ext 30048 WRH Bleep 398 or 491 Alex Bleep 0192
Oncology Consultant On-call (24 hours)	Via Switchboard

7. TRAINING

Oncology consultant presentation to acute medical staff and oncology medical team.

Training for nursing staff covering OOH acute oncology service by acute oncology nurses.

Training regarding administration and management of side effects is also included in the annual chemotherapy update for nurses.

8. REFERENCES

Nivolumab Dosing Administration and Safety Guide (2016) Bristol-Myers Squibb

Pembrolizumab Important Safety information to Minimise the Risk of Immune-Related Adverse Reactions (2016) Merck Sharp& Dohme

https://www.medicines.org.uk/emc/medicine/30602

https://www.medicines.org.uk/emc/medicine/30476

With thanks to Jo Upton, Immunotherapy Nurse, Clatterbridge Cancer Centre Foundation Trust

9. MONITORING TOOL

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
	All patients with immune-related reactions receive appropriate and timely management	Audit to monitor compliance with guidance	After 6 months	Immunotherapy nurse / Lead Chemotherapy Nurse	Haematology/Oncology directorate	Annually

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Appendix 1

Immunotherapy Out of Hours Checklist

Patient Name:_____ ID No:_____

Immunotherapy Agent: Ipilimumab / Pembrolizumab / Nivolumab (circle) Cycle no:_____

Date of assessment:_____ Time:_____

Immunotherapy can cause severe and fatal immune-mediated adverse reactions, the majority of immune-m mediated reactions occur over the course of treatment; however, they can occur weeks to months after discontinuation of treatment. It is important to recognise and address symptoms early.
Use this checklist for any out-of-hours calls from patients to identify signs and symptoms associated with immune-related adverse reactions.

- **ASK THE PATIENT ABOUT THE FOLLOWING SIGNS OR SYMPTOMS**
- **IF ANY OF THE ANSWERS COME INTO THE RED BOXES, THE PATIENT MUST BE SEEN, EITHER ON THE WARD OR VIA A+E**
- **If no responses are red, discuss urgently during the day time with the patient's consultant if available, or the registrar or consultant on call. Further assessment may need to be made.**

GENERAL	Response		Details
Are you able to perform your normal activities?	Yes □	No □	
Do you have a high temperature?	Yes □	No □	
- If yes, what was the temperature?			
Are you having headaches?	Yes □	No □	
Have you felt dizzy or light-headed?	Yes □	No □	
Have you noticed changes in your vision? If yes, how?	Yes □	No □	
Has your appetite changed? If yes, how?	Yes □	No □	
GASTROINTESTINAL			
Are you nauseated and/or vomiting?	Yes □	No □	
How many bowel movements are you having each day?			
- Is this different than normal? - If yes, how?	Yes □	No □	
- Are your stools loose or watery, or do they have a foul smell?	Yes □	No □	
- Are you doing anything to manage it? - If yes, what?	Yes □	No □	
Are you having cramping?	Yes □	No □	
Are you having pain in your belly? If yes, where?	Yes □	No □	
Have you seen blood or mucus in your stools?	Yes □	No □	
Are you able to pass urine?	Yes □	No □	

Is the colour of the urine brown?	Yes □	No □	
SKIN			
Does your skin itch?	Yes □	No □	
- If yes, is it keeping you up at night?	Yes □	No □	
Do you have a rash? If yes, where?	Yes □	No □	
- If yes, what are you using for it?			
Have you noticed that your skin is turning yellow?	Yes □	No □	
NEUROLOGICAL			
Are you having weakness in your hands or legs?	Yes □	No □	
Have you noticed that you are dropping things?	Yes □	No □	
Are you having difficulty walking or are you unsteady?	Yes □	No □	
Are you having numbness or tingling in your hands or feet?	Yes □	No □	
Are you having trouble picking things up?	Yes □	No □	
RESPIRATORY			
Have you been having any flu-like symptoms?	Yes □	No □	
Have you felt breathless at all? - If yes, when? - What were you doing?	Yes □	No □	
Is this different from normal? - If yes, how?	Yes □	No □	
Do you have a cough?	Yes □	No □	
Are you expectorating any phlegm?	Yes □	No □	
If yes, provide description:			
Does your chest feel tight?	Yes □	No □	

Assessing Nurse:_____ Signed:_____

Adapted from:
Clatterbridge Cancer Centre Checklist
YERVOY (ipilimumab) NURSING IMMUNE-MEDIATED ADVERSE REACTION CHECKLIST