Gloucestershire Safety & Quality Improvement Academy

Gloucestershire Hospitals NHS
NHS Foundation Trust

Management of Immunotherapy - related Diarrhoea/Colitis

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Background & Problem:

Monoclonal antibodies targeted against the immune checkpoint molecules CTLA-4 and PD-1 are increasingly being used for management of cancers. However, management of immune-related adverse events (irAEs) remains largely unknown to medical community. Although severe irAEs remain rare, they can become life-threatening if not anticipated and managed appropriately.

Aim:

Improving recognition and early management of immunotherapy related diarrhoea/colitis and improving referral for specialist review.

Methods:

Patients commenced on Immunotherapy between Jan 2017 and Dec 2018 were identified from pharmacy database (OPMAS). In patients admitted with colitis were identified from discharge summaries. Data extracted from discharge summaries, ICE and inpatient notes.

Results:

267 patients are commenced on Immunotherapy. 19 patients admitted with Diarrhoea/ Colitis. 14 patients are on Combination Immunotherapy and 5 patients on single agent. The patients who admitted with Diarrhoea/Colitis, 100% had their blood tests, 89% had CRP, 84% patients stool sent for C.Difficle,27% patients had documented grade on admission,92% started on high dose steroids and discharged on high dose tapering dose steroids and follow up. 72% patients who had G3/G4/persistent G2 were referred to GI team. 26% patients who had been commenced on combination immunotherapy has been admitted with Diarrhoea/ Colitis.

- Blood sample (FBP,U&E,LFT's) – 100%
- CRP – 89%
- Stool for C.difficile – 84%
- **Graded on admission – 27 %**
- Started on High dose steroids on admission/appropriately : 92 %
- **Referred to GI (Persistent G2 not improving / G3/ G4) : 72%**
- Discharged on High dose prednisolone with tapering Dose if appropriate – 100 %
- Follow up in Clinic – 100%

Conclusion:

Improvement needed in documenting and assessing grade of toxicity as treatment depends on this. Referral to GI specialist should be done without delay for persistent G2/ G3/G4 as there is evidence of decrease morbidity and mortality. This project caused the awareness about high rates G3/G4 toxicity with combination immunotherapy. It lead to creation of patient leaflets and leaflets to GP to cause awareness for early recognition and treatment of toxicity to limit duration and severity of irAE's . Created Helpline action cards and Guidelines Management of Immunotherapy adverse related event which are currently on Intranet. We would like to assess again in 2 years' time for improvement.
https://www.gloshospitals.nhs.uk/gps/treatment-guidelines/management-immune-related-adverse-events-iraes-caused-immunotherapy

TABLE 4. General Principles of Management once toxicity identified and graded
1. **NOTIFY CONSULTANT ON-CALL**+/- patient's TREATING ONCOLOGIST/ HAEMATOLOGIST of reported/ observed toxicity that is potentially an immune-related adverse event.
2. **ADMIT patients with grade 3 - 4 toxicity** and investigate (see reference 1, ASCO Guidelines) Consider admission for grade 2 toxicity if this is persisting and/ or hospitalization deemed safer.
3. **REFER TO ORGAN-SPECIFIC GUIDELINES** (ASCO, ESMO as referenced below- *Oncology/ Haematology Treatment Guidelines for organ-specific IR-AEs in progress).* Depending on individual toxicity consider CT imaging (for colitis/ pneumonitis), endoscopy (for colitis), cultures (stool, c. diff, septic screen), viral serology (for hepatitis), full endocrine profile +/- MRI pituitary (for endocrinopathies), ECG/ troponin/ Echo (for cardiac)
4. **LIAISE with relevant specialty** (e.g. dermatology, gastroenterology, endocrinology, etc.) about patients with grade 3 - 4 toxicity and consider also liaising about patients with persistent grade 2 toxicity.
5. **COMMENCE high-dose corticosteroids when necessary (as per Algorithm in TABLE 3)** with oral prednisolone or iv methylprednisolone; latter preferred if rapid symptom control warranted in a decompensated patient or oral intake/ absorption compromised. Convert to oral prednisolone after 2-3 days of iv methylprednisolone; then reduce by 10mg/ week (TABLE 6b).
6. **MONITORING while on steroids:** • Capillary blood glucose and BP • Avoid proton pump inhibitors unless gastric symptoms develop • Consider PCP prophylaxis if on prolonged steroids (e.g. >20mg for >4weeks) • If diabetic use bd dosing for oral prednisolone • If diabetic treat hyperglycaemia with oral hypoglycaemics/ insulin
7. **ALERT ON CARDIOVASCULAR TOXICITIES AND ALL FATALITIES by regimen/ toxicity: see TABLES 5a and 5b**

TABLE 3. ALGORITHM	
Toxicity Grade (NCI CTCAE v5)	When to interrupt ICPi, when to commence steroids, when to rechallenge
1	Continue ICPi with close monitoring EXCEPT for: Underlined Neurologic, Cardiac, Haematological toxicities (see table 2)
2	HOLD ICPi for NEARLY ALL toxicities AND CONSIDER STEROIDS (For Lymphopenia, Haemolytic uraemic syndrome may continue) Prednisolone 0.5-1mg/kg/day or equivalent Rechallenge when toxicity (incl. labs) reverts to grade 1
3	HOLD ICPi for ALL toxicities AND START STEROIDS Methylpred iv 1-2mg/kg/day or Prednisolone 1-2mg/kg/day or equivalent If no improvement after 48 to 72 hours: Consider additional immunosuppressive treatment in some toxicities (see note below) Steroid taper: Over at least 4-6weeks Rechallenge: Consider if reverts to grade 1 (cautious in early-onset irAE)
4	DISCONTINUE ICPi for ALL toxicities AND START STEROIDS Methylprednisolone iv 1-2mg/kg/day If no improvement after 48 to 72 hours: Consider additional immunosuppressive treatment in some toxicities (see note below) Steroid taper: Over at least 4-6weeks Rechallenge: Only endocrinopathies if controlled with hormone replacement

Aim	Primary Drivers	Secondary Drivers	Change Ideas
Improving recognition, early management, referral of patients with acute immunotherapy related colitis	Awareness of clinical staff	Staff education	Educational/Departmental meetings – Linking with ED Regular updates E mail updates
		Intranet pages	- under oncology - under GP trust website - under ED guidelines
		Posters	Put up - Oncology helpline - ED - Chemo unit
	Guidelines	Available on intranet	Place on intranet with supporting information
		Locally approved guidelines	Need to be approved by local policy approval group & involved med specialities eg: GI,Resp, Endocrine
	Patient awareness	Information Leaflets/Action cards	Ensure patients given PIL
		Medi-alert cards	Give to patients to give their GP/ED in acute setting
		Whom to contact – Oncology helpline	Pre Immunotherapy education session
	Access to services	Channel patients to oncology	Sign post patients to chemo helpline Sign post staff to AOS services
		Improve the time to specialist assessment and management	
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References:

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http://ascopubs.org/doi/pdfdirect/10.1200/JCO.2017.77.6385
2. Haanen JBAG et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 28 (S4); iv119-142, 2017 **https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from- Immunotherapy**
3. Thames Valley Immuno-oncology agent immune-related adverse event clinical guideline, v1.0- April 2017
http://tvscn.nhs.uk/networks/cancer/cancer-topics/chemotherapy/