Secondary complications of drug-related immune-mediated adverse events in clinical trials, patient case study

Patient Medical History

Darren 59 yo male

- Background Hx – C282Y heterozygous mutation
- Family Hx – mother with metastatic melanoma 2016 (brain/lung) treated with surgery/XRT/Pembrolizumab. In CR.
- Excision of Level 4 melanoma L thigh 07/2019 (SLN –ve)
- 10/2022 – 2 months L inguinal mass. Biopsy confirmed metastatic melanoma (BRAF -ve)

Darren enrolled in a clinical trial and commenced on a histone deacetylase inhibitor investigational product in combination with a PD-1 inhibitor. Seven cycles completed prior to onset of drug-related pneumonitis.

Rapid deterioration occurred when patient was overseas for business with exacerbation of dyspnoea and significant weight loss. Following communication with site staff, patient was urged to seek immediate medical attention.

Diagnosed transverse myelitis and hypoxic respiratory failure related to exacerbated drug-related pneumonitis.

Nivolumab - What is it?

Immune checkpoint inhibitors have become the first-line treatment for melanoma and many metastatic solid tumours as they are efficacious and generally well-tolerated. Nivolumab is a fully human, monoclonal igG4 antibody that binds to the programmed death-1 (PD-1) receptor to relieve immune suppression factors. The PD-1 inhibitor enhances T-cell activity by allowing T-cell receptors to recognise antigens on the cell surface facilitating tumour cell destruction by the host immune system. However, abnormal activation of autoreactive T-cells can lead to inflammation in any organ system. The lungs are one of the most commonly affected organs with pneumonitis a serious pulmonary toxicity associated with high morbidity rates. Neurologic immune-related adverse events rarely occur and are challenging to identify due to their subtle presentation and varying symptoms. Although checkpoint inhibitors aim to elicit an amplified immune response, it can go awry leading to permanent side effects as those seen in Darren's case.

Communications with Darren

- Triaged via email whilst overseas.
- Initial barriers overcome to organise a safe, urgent health plan whilst in Southeast Asia.

10/2022
Diagnosis Metastatic Melanoma

06/2023
Cycle 7 Day 1 patient reported reduced aerobic exercise with mild exertional dyspnoea.

06/2023
Echocardiography

07 & 08 /2023
Patient was managed by Respiratory for weaning of steroidal therapy. Communication between Respiratory and patient to continue management of patient and the adverse events (AE).

08/2023
Clinical Trial reporting to safety for the Severe Adverse Event (SAE)

- Unblinding processes with Clinical Trial Sponsors initiated due to required treatment interventions needed immediately in hospital.
- Communications between Principal Investigator/Medical Oncologist, Clinical Research Associate, Sponsor, Medical Monitor, Clinical Research Nurses, and Hospital.
- Unblinding performed by Principal Investigator/Medical Oncologist after consultation with Sponsor & Medical Monitor as is pertinent to the clinical setting for safety purposes.

14/08/2023
Discharged from Hospital. 12 days stay.

08/2023
Neurology / Respiratory / Immunology / Medical Oncologist. Treatment ongoing Rituximab and Prednisolone 5mg.

02/2024
Pneumonitis slowly improving and stable neurology. No evidence of progressive disease.

Goals of collaboration

- Improving overall lung capacity, allodynia, and gait.
- Continued outpatient support to recover weight muscle mass.

11/2022
Commenced on clinical trial: histone deacetylase inhibitor investigational product in combination with a PD-1 inhibitor.

06/2023
Multidisciplinary – Referral to **Respiratory Specialist** for review. Lung Function Test and was diagnosed as Asthma initially. **Treatment – Symbicort 200/6 BD**

07/2023

- CT performed 04Jul2023. Diagnosis of Drug Related Pneumonitis.
- Clinical Trial paused and nil further administration of histone deacetylase & PD-1 inhibitors.
- Commenced on Prednisolone 50mg OD as per Respiratory specialist 06Jul2023.
- PPI and Antibiotics commenced 06Jul2023.
- 07Jul2023 Bronchoscopy performed to exclude atypical infections. Results NAD. Consistent with Drug Related Pneumonitis.

08/2023
Rapid deterioration occurred when patient overseas for business in Southeast Asia.

- 02Aug2023 admitted to hospital.
- Diagnosis - Hypoxia / Immune Related Pneumonitis / Transverse Myelitis
- Multidisciplinary – Emergency / Neurological / Respiratory / Immunologist / Cardiology / General Surgical / Oncology / Clinical Trials

08/2023
Given methylprednisolone + cyclophosphamide for pneumonitis. IVIg + rituximab for transverse myelitis.

23/08/2023
End of Trial visit due to toxicity – pneumonitis and transverse myelitis

- Significant muscle loss
- mild ataxic gait
- Respiratory Lung Function improving
- Having ongoing IVIg + rituximab being managed by immunology department.

10/2023

- Ongoing neuropathic symptoms.
- Respiratory symptoms stable.
- Activities limited by neurology.

Multidisciplinary input

- Created networking links between both the Private and Public Health sectors
- Barriers identified in real-time communication with both sectors

Clinical Trials communications

- Safety reporting team, trial company, trial medical monitors, trial research associate and ethics committee
- SAE follow-ups reported to communicate and update on patient status.

Darren's Side Effects

Drug related pneumonitis

Darren initially showed reduced aerobic exercise capacity with mild exertional dyspnoea. No cough and nil infective symptoms.

A CT scan and bronchoscopy diagnosed him with drug related pneumonitis.

His dyspnoea increased, until commencement on steroidal treatment. Breathing became easier on steroidal support.

He went on a work trip overseas at this time and through email communication with trial coordinators communicated his health concerns.

He reported vomiting black substances, black stools, increased shortness of breath, significant weight loss of 16kg and fatigue. Trial coordinators discussed with Principal Investigator/Medical Oncologist for the trial and Darren was told to go to emergency overseas as soon as possible. Darren decided not to do this and returned to Australia.

On arrival back in Australia he presented to emergency where he was diagnosed with severe hypoxemic respiratory failure and worsening pneumonitis.

Transverse myelitis

In hospital Darren proceeded to develop sensory changes with a T5 level and right sided allodynia. MRI spine was performed with long segment intramedullary T2 hyperintensity within the central cord extending from T1-T10 maximally at T4 congruent with suspicion of transverse myelitis.

Immune related adverse event (IRAE) colitis

Darren reported diarrhoea on admission to hospital. Flagged concerns as potential IRAE colitis. CT Abdo and pelvis was ordered with nil bowel mucosal thickening or mesenteric fat stranding. This showed nil evidence of enteritis or colitis; however, it was reported that this remained as a clinical possibility due to symptoms with ongoing monitoring.

Patient Hospital Journey

Multidisciplinary collaboration occurred between emergency, cardiology, respiratory, neurology, immunology, general surgical, oncology, and the clinical trials team to coordinate the below assessments.

Assessments:

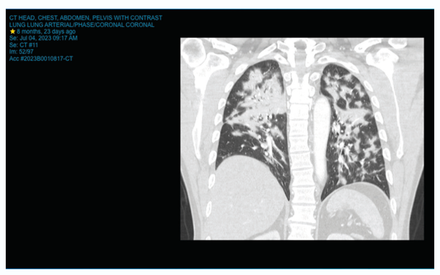
CT pulmonary angiogram
Extensive pathology
COVID PCR and respiratory panel
Hepatitis BcAb positive
CT Abdomen and pelvis
MRI Whole spine
Transthoracic echocardiogram
Colonoscopy

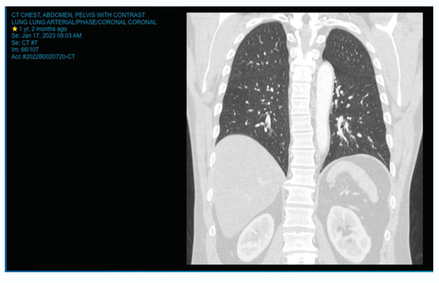
Treatment:

Emergency department:
- Hi-flow oxygen
- Methylprednisolone

Intensive care:
- Rituximab
- Cyclophosphamide
- Immunoglobulin
- Antiviral (entecavir) prophylaxis for 12 months
- Antibiotic (trimethoprim/sulfamethoxazole) for Pneumocystis jiroveci Pneumonia prohylaxis

Outpatient:
- Immunoglobulin
- Rituximab
- Weaning plan for prednisolone
- Regular imaging
- Monitoring for secondary complications of chronic steroid use
- Liver function 1 week post discharge
- Follow-up with neurologist, respiratory, immunology, oncology and principal investigator/ medical oncologist





Clinical trial reporting pathway

On identification of dyspnoea, referral to Private Respiratory Specialist was organised. Communications initiated with Sponsor Clinical Research Associate (CRA) and Trial Head Sponsor as patient did not have private health insurance and unknown potential costs as trial related investigations were required.

Upon diagnosis of Drug Related Pneumonitis, further communications held with the Sponsor Medical Monitor and Principal Investigator/Medical Oncologist. Cessation of trial related treatment was decided.

Darren was overseas when a further deterioration to his health status was noted and influenced his return to Australia leading to his hospitalisation. Serious Adverse Event (SAE) form was filled out and lodged with Medical Safety and University of the Sunshine Coast (UniSC) Ethics, within the 24hr reporting window. First SAE submitted was for Hypoxic Respiratory Failure.

Clinical Trials team liaised with the Public Hospital to ensure a definitive diagnosis and ongoing plan of care was established along many timepoints throughout Darren's journey.

The Public Hospital informed Clinical Trial Team of a secondary diagnosis of Transverse Myelitis. Second SAE submitted for Transverse Myelitis to Clinical Trial Medical Safety and UniSC Ethics.

There were multiple follow ups performed in each SAE submission as further results became available. Intense De-Identification of reports/results prior to sending any follow up to Clinical Trial Medical Safety to ensure Good Clinical Practice (GCP) guidelines were followed.

During Darrens hospital admission it was pertinent to unblind his randomisation to verify the oral component of the clinical trial to eliminate any drug related interactions. The sponsor gave permission to unblind, and this was solely performed by the Principal Investigator/Medical Oncologist to eliminate any potential drug related interactions.

Reflections for practice

On reflection, we looked at adapting the eviQ immunotherapy patient assessment tool, into a patient self-assessment health questionnaire specifically designed for our clinical trials. This was discussed with our ethics and quality teams, however, as it is patient facing material it is required to go for central ethical approval. With this information we modified the self-health questionnaire into a reference guide for nurse assessment of trial specific adverse events.

This will assist early identification and reduce secondary complications of immune-mediated conditions.

UniSC Clinical Trials

Oncology and haematology Clinical trials

Nursing assessment guide

Pre-treatment checklist

Check the safety labs are within protocol window
Check the safety labs are within protocol defined limits
Has the patient completed the trial specific questionnaires
Check patient investigational product (IP) compliance
Has the patient diary been completed
Has the patient taken any new concomitant medications since their last visit
Has the patient had any concomitant procedures
Has the patient had a scan and has RECIST been completed by the Principal investigator
Are any central blood to be collected this visit

Specific adverse events below if yes to any fill in Adverse events log and discuss CTCAE grading with Principal Investigator

Are you experiencing any nausea or vomiting?
Any changes to your bowel movements?
Do you have changes in appetite or thirst?
Do you have any mouth ulcers?
Are you experiencing any changes to your urine? Odour, frequency, colour, blood
Have you had any bruising? More often than normal?
Have you noticed any changes to your skin? Rash, blisters, peeling, itching
Do you have any pain? Back, abdominal, chest
Do you have any shortness of breath?
New or worsening cough?
Do you have episodes of dizziness?
Have you noticed any swelling in your legs or feet?
Do you have any numbness/tingling in your hands or feet?
Do you have left or right sided weakness
Has your balance or walking changed?
Have you noticed any changes in your vision? Blurred or sensitivity to light
Have you noticed any changes in your memory?
Have you noticed any changes to your mood? Anxious, irritability, depressed
Do you have chills?
Have you had a temperature >38 degrees?