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Management of Immunotherapy Related Adverse Effects

Abstract

Background: Over the last 5 years ever since Ipilimumab received FDA approval for the treatment of metastatic melanoma, immunotherapy as a treatment modality is making its presence felt in oncology clinics across the globe. While initially approved for the treatment of metastatic melanoma alone, the immunotherapy repertoire is ever expanding with its' utility being assessed for in the metastatic and adjuvant setting. The adverse effect profile from immunotherapy drugs differs from that of conventional chemotherapy that oncological services have trained in managing over the last few decades. This raises the need for educating health care professionals as the scenarios that patients present with at acute admissions or in clinic secondary to immune related adverse effects (iRAEs) can often be misleading.

Aims: This review aims to synopsise the common and less common iRAEs and highlight their varied presentations, in addition to stressing the need to institute timely immunosuppression, which forms the cornerstone in the management of iRAEs.

Recommendations: iRAEs have been recognised more frequently and in greater severity in dose dense and combination treatment regimens. While dermatological, gastrointestinal, hepatic toxicities in addition to endocrinopathies are the most commonly encountered iRAEs though other organ systems can be involved. The appropriate grading of an iRAEs' severity, delaying or discontinuing immunotherapy based treatment, supportive care, commencement of immunosuppression (with corticosteroids and/or steroid sparing agents) and a multidisciplinary approach are key constituents in the treatment pathway of iRAEs.

Conclusion: Early recognition of iRAEs and timely commencement of appropriate immunosuppression is imperative in order to reduce the risk of significant morbidity and potential mortality. The management of iRAEs warrants a multidisciplinary approach which would be aided by the development of local guidelines and educational activities directed at providing health care professionals with the information and tools required to recognise and appropriately treat iRAEs.

Review Article

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Introduction

Over the last few decades there has been an increasing interest in the field of cancer immunotherapy. The manipulation of the immune system using immunotherapeutic interventions has changed the therapeutic landscape in many type of cancers [1-4]. However, immunotherapy carries immune-related adverse effects (irAEs) which can be significant [5-7]. irAEs are usually reversible but occasionally can be life-threatening [5-7]. A retrospective study on the irAEs of Ipilimumab showed that 85% of patients experienced irAEs of any grade of whom 19% discontinued therapy [8]. 35% patients required systemic corticosteroids and 10% required anti-TNF therapy for irAEs [8]. There were no significant differences in overall survival in those with and without irAEs or between those who received corticosteroids or not [8,9]. Hence, this requires the development of treatment protocols and training of the healthcare professionals in the recognition and management of irAEs.

Common Side Effects

Dermatological toxicity

Dermatological toxicity from immune checkpoint inhibitors (ICPI) is the most common irAE [5] and usually develops within the first 10 weeks of immunotherapy [10] in any tumour type [11,12] with a small percentage of patients developing delayed skin toxicity [13]. The incidence of any grade rash is of the order of 24.3% in patients treated with Ipilimumab of which 2.4% experienced grade 3 and 4 rash [12], 25.4 % in patients treated with anti-PD-1 therapy alone and 40.3% in the anti-CTLA-4 and antiPD-1 combination treatment [2]. Clinically, the rash manifests as erythematous, reticular, maculopapular, nodular or lichenoid eruption with or without pruritus [14] or hypopigmentation on the extremities and trunk with the palms, soles and head being speared in the majority of the cases [11,15,16]. Less commonly it presents as bullous eruption [17].

Vitiligo is another dermatological irAE which occurs in approximately 10% of patients with advanced malignant melanoma with a higher frequency in patients treated with Pembrolizumab and Nivolumab rather than Ipilimumab [5,7,18,19]. It is usually developed in the upper limbs [5,18] at least 3 weeks after the commencement of ICPI [10]and correlated with longer progression free survival in patients treated with Pembrolizumab [9,18]. Vitiligo has not been reported in lung and renal cancer patients [1,3,20] and a possible explanation is that both the skin and the melanoma cells share the same antigen, Melan-A which results in transient inflammatory response [11].

On the other hand, the incidence of pruritus ranges between 6 and 20% in patients managed with anti-PD-1 inhibitors and up-to 35% in patients treated with Ipilimumab with higher frequency in melanoma rather than other malignancies [2,4,19]. Rare dermatological toxicities include Stevens Johnson syndrome, toxic epidermal necrolysis [7,10,21] drug rash with eosinophilia and systemic symptoms (DRESS) [21] and sweet syndrome [22]. These severe adverse effects are more frequent in anti-CTLA-4 and anti-PD-1 immunotherapy combination with an incidence of 4.8% [2].

The initial management of dermatological toxicities depends on the severity based on the body surface area (BSA) [7]. For instance in grade 1 rash, namely localised rash or pruritus (less than 10% BSA), topical corticosteroid creams of medium to high potency, sun protection creams as well as oral antihistamines can be used [5,7,14,23]. Pruritic symptoms can also be relieved with the use of cold compresses, oatmeal baths as well as oral or topical doxepin hydrochloride or oral aprepitant if the active daily living activities have been affected [5,11,23]. If the rash is stable or responding to the local treatments, ICPI can be continued [7].

Moderate severity rash, namely grade 2 (10-30% BSA), can be managed as grade 1 if the symptoms are tolerable [7,14]. Otherwise, oral prednisolone (0.5-1mg/kg/day) can be initiated which should be tapered and reassessed within one to two weeks [7,14]. The treatment should then be delayed until the rash improves to grade 1 or lower and the patient is on less than 10 mg of prednisolone or equivalent, daily [5,7,14]. In the event of persistent or recurrent grade 2 rash, immunotherapy should be withheld and a skin biopsy should be considered [7].

In patients with grade 3 rash (>30% BSA), the treatment should be withheld until the rash resolves to grade 1 or lower, and the patient should be treated with intravenous corticosteroids (1-2 mg/kg/day of methylprednisolone or equivalent) which should be weaned off within four weeks [7,11,13]. In addition, dermatological advice should be sought for consideration of skin biopsy [7]. The use of immunosuppressive drugs such as infliximab should be considered in cases which are unresponsive to corticosteroids [5]. Finally, in rare cases, such as Stevens Johnson syndrome and toxic epidermal necrolysis, a multidisciplinary approach should be followed in conjunction with the dermatology and critical care teams. These patients should be admitted in hospital for supportive care with intravenous fluids and electrolyte replacement and the drug should be permanently discontinued [5,7,11,23].

Gastrointestinal toxicity

Gastrointestinal toxicity either in the form of diarrhoea or colitis, is an important element of the toxicity profile of ICPIs in view of the significant associated morbidity and potential mortality. Diarrhoea is the most common form of the iRAEs. While diarrhoea is defined by the increase in frequency or change in the consistency of stool, colitis is often in this clinical scenario defined by the presence of abdominal pain or tenderness, presence of blood in stool or radiological evidence of large bowel inflammation. Inflammation of the small bowel is uncommon but has been reported with the use of ipilimumab [24]. Mortality has been reported in 1% of cases i.e. in individuals treated with Ipilimumab at 10mg/kg and thereby highlights the need for the timely assessment and institution of appropriate immunosuppressive therapy [25,26].

Clinical data indicates that the incidence of diarrhoea of any grade is significantly higher with the use of CTLA-4 antibodies at approximately 28% as compared to 15% with the use of PD-1 antibodies. Combination treatment with Ipilimumab and Nivolumab increases the incidence of diarrhoea to approximately 44% (Table 1) [7]. The incidence of gastrointestinal toxicities is linked to the dose density of the CTLA-4 or PD-1 inhibitors administered and are more frequently manifested in with combination treatment. Table 1 outlines the frequency of diarrhoea/colitis based on drug regimen.

Table 1: Frequency of diarrhoea/colitis based on treatment regimen.

Drug Regimen	Any Grade	Grade 3-4	Colitis
Ipilimumab 3mg/kg every 3 weeks	28%	8%	5%
Nivolumab 3mg/kg every 2 weeks	15%	1%	<1%
Pembrolizumab 2mg/kg every 2-3 weeks	15%	2%	2%
Ipilimumab + Nivolumab (3mg/kg + 1mg/kg every 3 weeks)	44%	9%	8%

Both diarrhoea and colitis are clinically manifested in approximately, 6 weeks of the commencement of treatment with Ipilimumab and Nivolumab unlike with the use of Pembrolizumab, where gastrointestinal toxicity may manifest up to a time period of 6 months [26,28]. It is important to consider that these timelines are not absolute as toxicities could occur earlier or later. Thus, the clinical context of the presentation should be considered in decision making.

A patient assessment should include a detailed clinical history and examination with information on the following points ascertained: time of onset of diarrhoea in relation to last ICPI treatment, frequency of loose stools per day, stool consistency, presence of blood in stool, association with abdominal pain/cramps, nausea, vomiting, rise in temperature, recent antibiotic use, recent travel in addition, history of other toxicities from

treatment with ICPI. When clinically indicated it is pertinent to rule out bacterial including clostridium difficile or viral infections.

A physical exam should include an assessment of haemodynamic stability and a complete clinical exam including abdominal and per-rectal exam. Baseline investigations should include routine bloods tests including haematology and biochemical profile, lactate, cortisol, thyroid function tests, and random serum glucose. Stool examination for ova and parasite as well as clostridium difficile assay should be requested if it is clinically indicated. An abdominal X-ray (AXR) would be helpful as it would provide evidence of perforation, bowel dilatation or bowel wall oedema which thereby suggests the presence of colitis. Endoscopy can be helpful in guiding treatment with early recognition of colitis especially in moderate namely grade 2 toxicity. The findings may include mucosal oedema with biopsies demonstrating neutrophilic, lymphocytic, or mixed neutrophilic-lymphocytic infiltrates [29]. Endoscopy may also be helpful in assessing response to immunosuppression namely resolution of inflammatory infiltrate after a period of treatment with corticosteroids. The management of gastrointestinal toxicity involves the use of anti-motility agents and immunosuppression with corticosteroids and it is based on the early identification of severe toxicity (Figure 1).

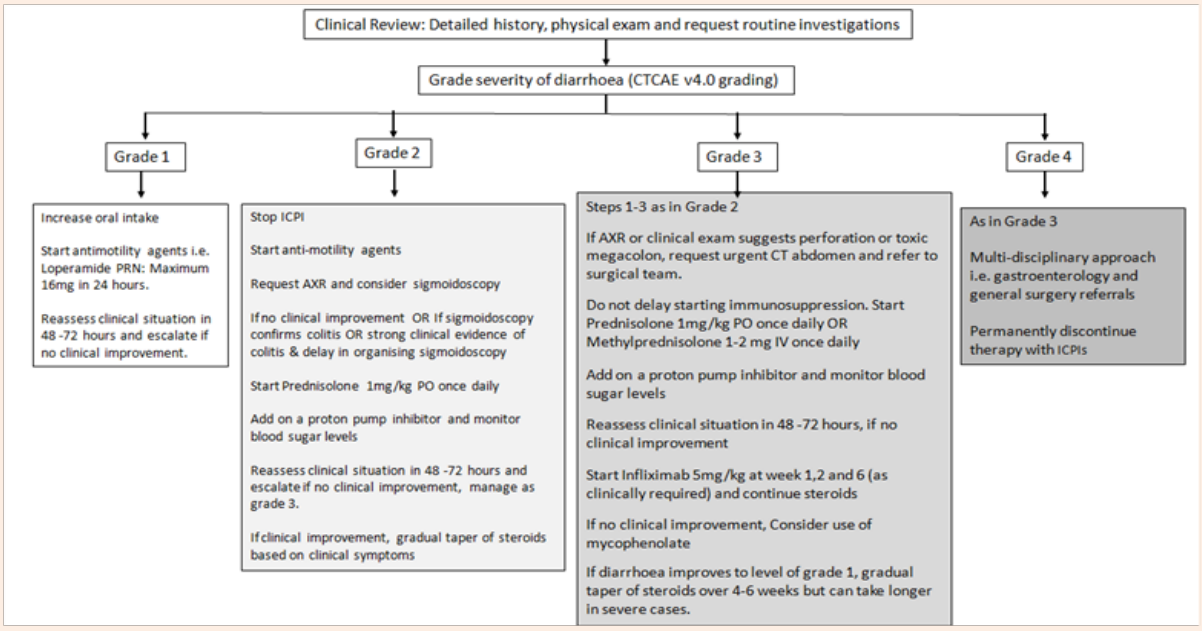

Figure 1: Proposed treatment approach to ICPI induced diarrhoea/colitis.

Hepatotoxicity

Elevations in serum aminotransferases i.e. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) has been observed with both CTLA-4 and PD-1 receptor blockade and usually occur between 8-12 weeks after commencement of treatment [10]. These elevations are often asymptomatic and not associated with a rise in bilirubin. Hepatotoxicity should be graded based on the severity in the elevation of the aminotransferases as demonstrated in CTCAE v4.0. The incidence of hepatotoxicity is dose related and (Table 2) indicates frequency of toxicity based on doses of check point inhibitor therapy.

It is important to closely monitor liver function tests (LFTs) while on treatment with CTLA-4 or PD-1 inhibitors. In the event of raised LFTs, it would be prudent to exclude viral and auto-immune causes as well as haemochromatosis as part of initial investigations should include:

Table 2: Frequency of hepatotoxicity based on treatment regimen.

Drug Regimen	Grade 3-4
Ipilimumab 3mg/kg every 3 weeks	1%
Nivolumab 3mg/kg every 2 weeks	2%
Pembrolizumab 2mg/kg every 2-3 weeks	1%
Ipilimumab + Nivolumab (3mg/kg + 1mg/kg every 3 weeks)	19%

a) Viral screen: Epstein Bar Virus (EBV), Cytomegalovirus (CMV), Hepatitis B & C, Hepatitis A, D & E if recent history of travel outside the United Kingdom.

b) Autoimmune screen: Anti-nuclear antibody (ANA), Anti-

neutrophil cytoplasmic antibody (ANCA), Anti–smooth muscle antibody (ASMA).

c) Iron studies.

An ultrasound of the liver may be helpful to rule out obstruction of the biliary tree as well assess for masses in liver parenchyma i.e. abscess, new diagnosis or confirmation of progression of previously identified liver metastases. While an ultrasound may not identify tell-tale signs of ICPI-associated hepatotoxicity, a CT scan may identify mild hepatomegaly, peri-portal oedema or peri-portal lymphadenopathy [30]. A liver biopsy is not indicated but if diagnostic ambiguity prevails it may be considered and would demonstrate severe pan-lobular hepatitis with prominent perivenular infiltrates with endothelialitis. A primary biliary pattern with mild portal mononuclear infiltrate around proliferated bile ductules has also been reported [31].

Usually immunosuppression with corticosteroids for 3 weeks or more is required with gradual taper in the corticosteroid dose, once severity of toxicity is grade 1 or lower. AST and ALT levels uncommonly do not respond to corticosteroid therapy and in these situations mycophenolate (500 mg – 1000mg every 12 hours) may be administered in addition to corticosteroids. Antithymocyte globulin (ATG) therapy may also be considered in a refractory setting [32]. It is important to remember that Infliximab should not be given to patients with elevated AST/ALT since infliximab carries a risk of hepatotoxicity.

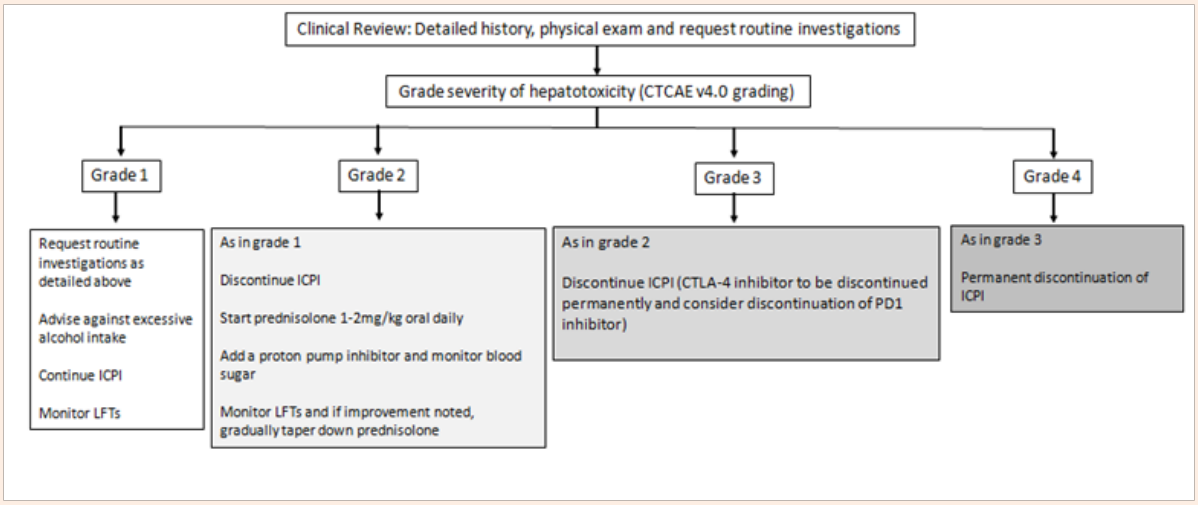

Figure 2: Proposed treatment approach to ICPI-induced hepatotoxicity.

Endocrinopathies

Endocrine irAEs occur in up to 10% in patients treated with Ipilimumab, Pembrolizumab and Nivolumab [1,2,5,7,19] and range from asymptomatic changes in thyroid function test to adrenal insufficiency [5,7,10]. The onset occurs in the weeks following the initiation of treatment with ICPIs, usually on average after 6 weeks for anti-CTLA-4 therapies and 10 weeks for anti-PD-1 antibodies [7,10] but a delayed onset has also been reported [33].

Hypophysitis

Hypophysitis is one of the most common endocrinopathies with higher incidence with combination of Ipilimumab and Nivolumab (8%) and with anti-CTLA-4 therapy alone (2-4%) rather than anti-PD-1 agents (less than 1%) [2,19,34].The diagnosis can be challenging because the patients may present with non-specific symptoms such as tiredness, nausea, headache, dizziness, mood changes, amenorrhea or impotence [5,10]. Associated features which can guide the diagnosis are unexplained hypoglycaemia and postural hypotension [5]. Thyroid function and clinical chemistry profile should tested regularly prior to each therapy because it may represent an early biochemical change [5,7]. In clinically suspected hypophysitis, the pituitary axis should be evaluated, namely the morning cortisol, the ACTH, TSH, LH, FSH, prolactin, testosterone in men and oestradiol in women [7]. MRI pituitary may contribute to the diagnostic process with the main findings being pituitary enlargement, abnormal enhancement or atrophy [10,24]. However, normal findings can also be seen when the MRI imaging is taken after the initiation of high dose corticosteroids [7].

The management of hypophysitis depends on the clinical symptomatology. For instance, asymptomatic patients should be treated with hormone replacement they are discussed with the endocrine team [7]. It is important that the cortisol replacement is initiated a week prior to the commencement of levothyroxine [7]. In symptomatic hypopituitarism, the ICPI should be withheld and intravenous methylprednisolone (1-2 mg/kg/day) along with intravenous fluids should be administered, especially in cases of adrenal crisis [5,7,10]. Although the high dose corticosteroids may reverse the inflammatory process and prevent the requirement for long term hormone replacement, the majority of the patients require permanent corticosteroid replacement [5,35]. The first should be switched to oral prednisolone (1-2 mg/kg/day) which should be tapered over 4 week period and followed by hormone replacement therapy [7,10]. A clinical and radiological improvement is noticed within few days [10]. Nonetheless, the

median time to resolution of symptoms and the substitution of hormone replacement treatment can be longer than 20 weeks [10]. Importantly, because of the risk of secondary hypogonadism, patients of childbearing age should be counselled accordingly [5].

Thyroid dysfunction

Hypothyroidism is the second most common endocrinological irAE [36]. It is more common with the combination of Nivolumab and Ipilimumab (15%) and anti-PD-1 agents alone (4-10%) compared to Ipilimumab alone (2-4%) [2,4,19,25]. On the contrary, hyperthyroidism is less common with an incidence ranging between 1 and 7% [7]. Subclinical or mild hypothyroidism is more common with a less than 1% of patients developing severe and life-threatening symptoms [2,4,19,25,36]. Most cases present as silent thyroiditis secondary to antithyroglobulin and antithyroperoxidase antibodies and hypothyroidism or after transient subclinical hyperthyroidism [33,36] and very rarely as a thyroid storm [37].

The management of irreversible hypothyroidism involves hormone replacement with levothyroxine which can be initiated at a dose of 1-1.5 mcg/kg /day and the immunotherapy can be continued with no discontinuation [5,7,36]. Symptomatic hyperthyroidism with tremor and tachycardia can be treated with beta-blockers or corticosteroids. Carbimazole or Iopanoic acid should be used in syndromes mimicking Graves' disease or thyroid storm, respectively [37,38].

Other endocrine irAEs

Case reports of Type I Diabetes Mellitus [39] and diabetic ketoacidosis [40] secondary to anti-PD-1 antibodies as well as primary adrenal insufficiency due to Ipilimumab have been described [33].

Less Common Side Effects

Neurological toxicity

Neurological irAEs have been reported in less than 2% of the patients who received Ipilimumab, Nivolumab and Pembrolizumab [41-45]. Melanocytes and Schwann cells are derived from the neural crest and share similar antigens [41-43]. Gangliosides expressed on melanocytes are highly immunogenic with subsequent antibody formation which may be responsible for initiating peripheral motor sensory neuropathies such as Guillain Barre Syndrome [41,43]. Also, in patients with ICPI-induced encephalitis, N-methyl-D-aspartate receptor (NMDAR) immunoglobulin G antibodies were detected in the cerebrospinal fluid which are also expressed on melanocytes [42,44]. Other neurological irAEs include Myasthenia Gravis-like syndrome [43], posterior reversible leukoencephalopathy [46], aseptic meningitis [21], radiculoneuropathy [47], transverse myelitis [43] and Bell's palsy [40].

Acute management includes discontinuation of ICPI and early administration of either oral prednisolone or IV methylprednisolone (1-2 mg/kg/day), depending on the severity of the symptoms, [41,43,45] which may result in complete neurological recovery [48]. Early specialist neurological assessment is also advised [7]. MRI spine and/or brain, nerve conduction studies and lumbar puncture may facilitate the diagnosis [41,43,45]. Plasmapheresis or intravenous immunoglobulin or supportive drugs such as pyridostigmine in the case of Myasthenia Gravis, may be required in cases which are refractory to corticosteroids [41,43,44]. In addition, in persistent grade 2 or severe cases, ICPI should be permanently discontinued [10,41,49-51].

Pneumonitis

Pneumonitis is a relatively uncommon irAE and reported in up to 5% of patients receiving treatment with Ipilimumab and in less than 5% of patients receiving Nivolumab or Pembrolizumab alone [7]. As with other irAEs combination treatment with Ipilimumab ad Nivolumab increases the incidence of pneumonitis to 5-10% [52-54]. The treatment of pneumonitis is based on the severity of the clinical manifestation.

It is imperative to maintain a low threshold for initiating investigations in patients being treated with CTLA-4 or PD-1 inhibitors who present new symptoms of dyspnoea or cough. Consider concomitant bacterial or viral infections and initiate investigations and treatment accordingly. A chest X-ray would provide invaluable initial information and a CT Chest to be considered to clarify the clinical situation.

A bronchoscopy may be helpful in excluding an infectious aetiology prior to considering immunosuppression. Management of pneumonitis secondary to ICPI would benefit from a multidisciplinary team approach with involvement of the respiratory and intensive care teams where required (Figure 3) [7].

Haematological toxicity

Immune-related haematological toxicities occur in approximately 4% of the patients treated with Ipilimumab and range from asymptomatic cytopenias to autoimmune haemolytic anaemia, acquired haemophilia A, pure red blood cell aplasia and disseminated intravascular coagulopathy [45,49]. In mild haematological disturbances, immunotherapy can be continued with close monitoring [5]. Otherwise, haematological and clinical improvement is noticed with the interruption of the ICPI and the administration of high dose corticosteroids (prednisolone 1mg/kg/day or equivalent). In refractory cases, resolution of the irAE occurred with the use of intravenous cyclosporine, immunoglobulin and ATG therapies [40,41]. In some cases where the diagnosis is unclear, a bone marrow biopsy may be required [6].

Ophthalmological toxicity

Ocular toxicity is rare with an incidence of less than 2% but it constitutes a well-recognised irAE which ranges from uveitis, conjunctivitis and iritis to ocular myositis [7,45,33]. Rare cases of Graves' ophthalmopathy with normal thyroid function and raised TSH-receptor antibodies have also been reported [38]. The management includes early ophthalmological assessment with topical corticosteroid eye drops for mild to moderate symptoms and oral prednisolone (1-2mg/kg/day) or equivalent in highly symptomatic cases [7].

Pancreatitis

Pancreatitis has been uncommonly reported with the use of ICPIs [40,38], however there appears to be no particular indication to monitor amylase and lipase while on treatment unless it is clinically indicated. Moderate elevation in amylase and lipase do not need to be treated with corticosteroids unless pancreatitis

is clinically suspected. ICPIs will need to be discontinued and immunosuppression with corticosteroids initiated. Alternative causes will need to be excluded utilising the relevant imaging modalities and investigations. Referral for surgical intervention should be considered when clinically indicated.

Renal toxicity

Renal toxicity secondary to treatment with ICPIs is uncommon and has been reported incidence of 0-4% [7]. The manifestations are varied and range from isolated rises in creatinine to interstitial or autoimmune nephritis. Monitoring of renal function while on treatment with ICPIs is recommended. If a rise in creatinine is identified, this should be graded based on CTCAE v4.0 in addition to quantifying proteinuria in order assess for nephritis. Grade 1 renal impairment can be treated with increasing hydration and discontinuing nephrotoxic medications, however ICPI can be continued provided that renal function remains stable. Grade 2 renal toxicity warrants the commencement of prednisolone 1mg/kg/day and discontinuation of treatment with ICPI [7]. It would be advisable to consult the renal team and rule out alternative causes. Grade 3 renal toxicity may warrant a renal biopsy [7] and would require a multidisciplinary team approach.

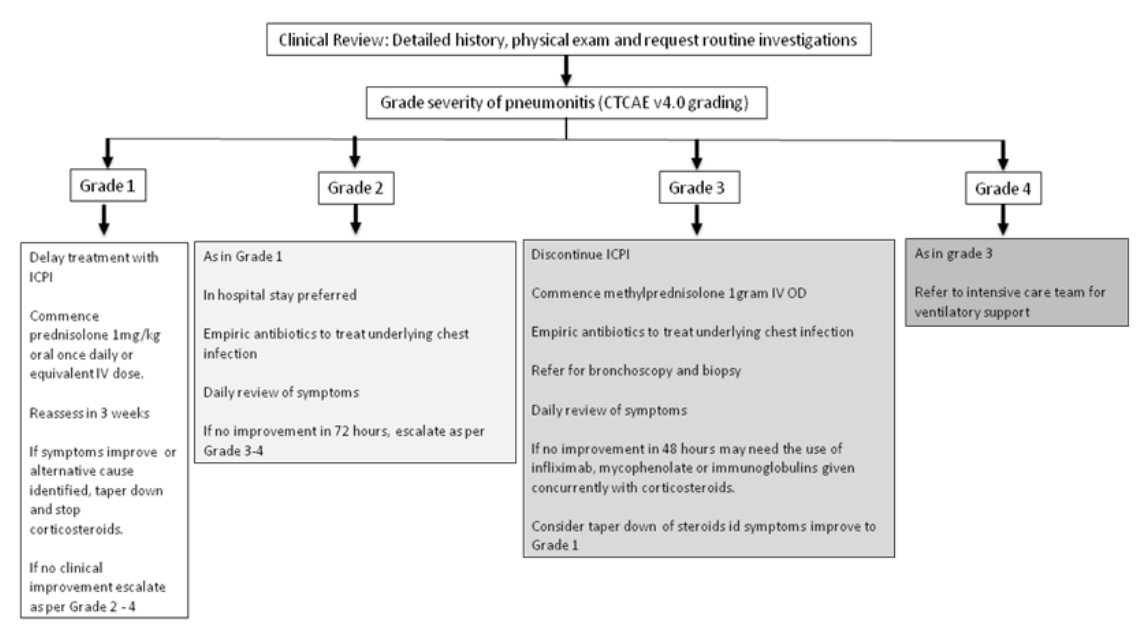

Figure 3: Proposed treatment approach to pneumonitis secondary to ICPIs.

Conclusion

The utility of immunotherapy based treatments is expanding to include a number of tumour groups in view of the potential durable response to treatment. The toxicities secondary to immunotherapy based treatments while generally transient can be on occasion severe and fatal. The management of toxicities revolves around the suspension of treatment with the ICPI and the commencement of systemic immunosuppression. Prednisolone 1-2 mg/kg/day (oral), is considered as adequate immunosuppression. This would have to be continued till the toxicities reduce intensity to Grade 1 and then gradually tapered down and discontinued. Patients presenting with Grade 3-4 toxicities secondary to immunotherapy-based treatment will have to have the treatment permanently discontinued. Resuming treatment with the same immune check point inhibitors or switching to an alternative agent should include careful consideration and an in depth discussion with the patient in view of the risk of recurrence of toxicities. If immunosuppression with corticosteroids is unhelpful, the addition of infliximab, mycophenolate or cyclophosphamide may need to be considered. Timely escalation to the primary oncology team and referral to the appropriate sub-speciality (gastroenterology, endocrinology, respiratory or dermatology teams) for clinical advice is encouraged.

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