Global management of patient receiving cancer immunotherapy

Francesca Mitjavila M.D.
Internal Medicine Department / Bellvitge University Hospital

Mechanisms of Immune related adverse effects

Immune checkpoint inhibitors are a novel class of drugs used in cancer immunotherapy that have improved overall survival in metastatic melanoma an other advanced stage cancers.

Cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed death receptor 1 and 2 (PD-1/PD-2)and PD-1 ligand serve to down regulate T cell proinflammatory responses thus allowing self tolerance and limiting self tissue damage. CTLA-4 and PD1 are exposed on the surface of T cells and Pd-L1 and PD-L2 are expressed on the surface of cancer cells are other immune cells. Inhibition of these immunological checkpoints leads to an overall anti tumour activity but can also be associated to the loss of self tolerance and excessive inflammatory responses. Immune related adverse effects (IrAE) are thus consequence of this activation of the immune system. The precise pathophysiology underlying immune-related adverse events (IrAE) is unknown. CTLA-4 inhibits the immune response in several ways, including attenuating T cell activation at an early step of the immune response, and PD-1 is believed to inhibit the immune response at later stages of the immune response in peripheral tissues. There are substantial differences in animal models. Mice lacking CTLA-4 die from lymphoproliferation, whereas mice lacking PD-1 develop different autoimmune organ damages. Immune related adverse effects form patients treated with anti CTLA-4 differ from those treated with anti PD1, and globally IrAE associated with anti CTLA-4 are usually more severe.
There are four main possible mechanisms underlying IrAE that are: 1) increased T cell activity against antigens that are present in tumours and healthy tissue. 2) Increased level of preexisting antibodies. 3) Increase of inflammatory cytokines and 4) enhanced complement mediated inflammation due to direct binding of an antibody against cytotoxic T lymphocytes.

Incidence and overview of main Immune related adverse effects

Incidence of IrAE ranges from 60-85% with anti CTLA-4 and 39-70% with anti PD1/anti PD-L1 agents. Combination therapy increases the risk with a RR of 1.5 compared to monotherapy High grade IrAE seems to be higher with ipilimumab (43%) compared to nivolimumab or pembrolizumab (20%). Treatment related death is about 2% but there does not seem to be a strong relationship between any single cancer and an associated severe toxicity. Moderate to severe IrAE tend to occur earlier with anti CTLA-4 than anti PD-1/PDL1 therapies.

Gastrointestinal: Diarrhoea and colitis are some of the most frequent IrAE, and are more frequent with anti CTLA-4 (30-40% of patients treated with Ipilimumab). they usually occur after more that6 weeks of therapy in severe cases. Colitis needs aggressive approach from the beginning with oral prednisone in grade 2 toxicity and iv glucocorticoids and infliximab in grade 3-4 toxicity. Hepatitis is much less frequent appearing in 2 to 10% of patients, being more frequent with combination therapy (15% G-3). It is important to rule out autoimmune hepatitis as infliximab is contraindicated in this setting.

Dermatologic: Dermatologic symptoms are common and appear in approximately 30-50%. they are more common with Ipilimumab (37-70%) than with anti PD-1 (17-37%). Grade 3-4 toxicities are rare (4%) but can be potentially dangerous.

Pulmonary: Pneumonitis is rare (2.7%) but it is associated to elevated mortality. It is mainly associated to anti PD1/PDL1. Its incidence is higher in combination therapy, where it can be up to 10. It is very low, < 1%, with anti CTLA-4

Endocrine: overall endocrine related adverse effects occur in 10% of patients treated. Thyroid dysfunction (mainly hypothyroidism) is more common in patients receiving anti PD1/PDL1 (4-10%) and hypophysitis occurs mainly in those receiving anti CTLA-4 (10-17%). Diabetes Mellitus leading to hyperglicemia and ketoacidosis is infrequent.

Rheumatologic: Up to 40% of patients refer arthralgia or myalgia, but the appearance of the novo severe rheumatologic diseases is not that frequent. Arthritis, polymyalgia-like syndromes, and myositis are the most common musculoskeletal manifestations

Cardiovascular: less than 0.1% of patients. May be greater with combination therapy. Immune-mediated myocarditis may result in heart failure or arrhythmia, and may be fulminant, progressive, and life-threatening.

Neurologic: incidence 3.8% in patients receiving anti CTLA-4, 6.1% in patients receiving anti–PD-1, and 12.0% in patients receiving combination. Severe events are less than 1% and involve CNS or peripheral nervous system. Headache and peripheral sensory neuropathy are the most commonly encountered symptoms.

Haematological: Anaemia occurs in 11% and grade3-4 in 5.8%. Thrombocytopenia in

8%. Other manifestations as TTP, acquired haemophilia are much less frequent
Others: Nephritis: 1-2%; Ocular: 1%

Immune related adverse effects in patients with preexisiting autoimmune diseases

Patients with autoimmune diseases (AID) have been excluded from clinical trials but we have some data from retrospective studies in patients with preexistent AID receiving immune checkpoint inhibitors for melanoma or non small cell lung cancer (NSCLC). Exacerbation of previous AID occurred in 23-30% of cases and approximately 30% of patients suffered an IrAE, not severe in most cases and needing discontinuation of therapy in a third of patients. All studies reported a higher proportion of flares in patients with rheumatologic AID than in other AID (40 to 10% approximately). IrAE were similar than in general population without AID. There was no relationship between immunomodulatory treatment for AID and response to immune checkpoint inhibitor or between the development of AID flare and response to immunotherapy. Response to cancer immunotherapy was similar to general population

Treatment of Immune related adverse effects

There are no prospective trials and most recommendations are based on consensus opinion.

Management of Grade 1 toxicities includes symptomatic treatment and in some cases delay checkpoint inhibitor. Grade 2 toxicities demand delaying checkpoint inhibitor administration and include oral glucocorticoids at low medium doses for most organ toxicities. In case of pneumonitis high dose prednisone should be administered from this stage. When grade 3-4 toxicities appear immune checkpoint inhibitor administration is usually permanently discontinue and management should include high doses of glucocorticoids and other immunosuppressant agents, mainly infliximab or other anti TNF, mycophenolate, Methotrexate, anti IL6, anti IL17, IvIG....Immunosuppressant agents should be administered early in some severe toxicities.

Additional risks of immunosuppression should be taken into account when evaluating theses patients. Frequently seen secondary effects of glucocorticoids are hyperglycemia, fluid retention, anxiety and osteoporosis. Calcium supplementation and vitamin D should be given to all patients receiving glucocorticoids. Opportunistic infections are also a main concern with an increased risk of aspergillus or pneumocystis pneumonia and cytomegalovirus hepatitis. Pneumocystis Jirovecii prophylaxis should be added to all patients receiving more than 20 mg of prednisone for more than 4 weeks. A review of 740 patients receiving 898 courses of immune checkpoint blockade for melanoma showed that main risk factors for teh development of a serious infection was the use of

corticosteroids (OR 7.71) and infliximab (OR 4.74).

Are Immune related adverse effects related to efficacy?

As the occurrence of IrAE provides evidence of that checkpoint blockade has activated patient's immune system one important question is whether the magnitude of immune activation increases the chances of success, and the general consensus is that these events are not required to obtain a benefit from treatment. On the other hand one could also think that the severity of IrAE could be a measure of the likelihood of a tumour response, but again this is not demonstrated except maybe in melanoma where vitiligo could be a sign of response.

Immunosuppression (IS) used to treat IrAE does not seems to modify reduce anti tumour efficacy. Data from retrospective studies have shown that outcomes of patients treated with IS for IrAE are not worse than those who did not receive IS for IrAE, but more studies exploring potential relationship between various aspects of immunosuppression (type, duration, timing) are needed.

Conclusions

- Early recognition and treatment is essential because severe IrAE can have a fatal outcome if not promptly and aggressively treated

- Need of patient and care giver education

- Need of multidisciplinary teams to address specific symptoms involving emergency physicians

- Aetiology and characterization of the different IrAE needs further research and definition