Review Article DOI: 10.18203/issn.2456-3994.IntJMolImmunoOncol20180469

Unforeseen consequences of cancer immunotherapy

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ABSTRACT

With the increasing use of immunotherapy for various cancers, it is essential that clinicians become aware of some of the unique consequences and sude effects associated with these new treatments. Ranging from pneumonitis and colitis to Type 1 Diabetes Mellitus, immune related adverse events have been reported. Some side effects may be confused with cancer progression and thus awareness and clinical presentation of these is critical and necessary in this fast moving field of medicine.

Key words: Immunotherapy, Autoimmune, Cancer immunology, Side effects, Adverse effects

Introduction

Manipulating checkpoint inhibition to treat cancer has arrived. The modality to unleash immune destruction on cancer cells is finding acceptance for a wide variety of cancers and seems to be on its way to become standard of care for the first line, subsequent lines, and even adjuvant settings. From lung, bladder, kidney, melanoma, and head and neck cancers to now lymphomas, the treatment is having good success rate and survivors galore. It is time to become aware of some of the unique consequences of unleashing immune therapies. Besides, pneumonitis and colitis that were earlier noticed, bizarre new developments like Type 1 diabetes mellitus have been reported.

Programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors are used alone and in combination. Adverse events seem to climb with prolonged use and when combined and seem to be appearing between 6 and 12 weeks after starting therapy. Lymphadenopathy or pneumonitis appears to be confused with cancer progression when they may actually denote response! It must be emphasized that these side effects are seen in <10% of patients and hence should be more vigilantly looked for. This is a complete paradigm shift from cytotoxic chemotherapy side effects such as nausea and marrow suppression that were the norm and seen immediately following chemotherapy.

Mechanism and Postulates

Immuno-oncology drugs complement the various other treatment approaches including chemotherapy, radiation, and targeted therapies. The immense advantages of these powerful immunotherapeutics are not without limitations including immunotoxicities and autoimmune reactions. The vast repertoire of immune-oncology drugs encompasses various antibodies, peptides, proteins, small molecules, adjuvants, bispecific molecules, cytokines, oncolytic viruses, and cellular therapies.[1]

The possible autoimmune complications of these drugs tend to be underestimated due to the often short follow-up period. Symptoms of autoimmune conditions can often be vague and are missed. Furthermore, we only come to know of autoimmune reactions in patients that survive. Many of the immune-related adverse effects (irAEs) manifest with noticeable symptoms many weeks or even years following treatment.

Our understanding of the underlying mechanisms as well as the relative susceptibility of different individuals to irAEs is in its infancy. The immune system has a complex, redundant, and robust "self-check" system. Immune tolerance is the intentional lack of lymphocyte reactivity to self-antigens. In the thymus, T-cell receptors (TCRs) undergo recombination resulting in a vast repertoire of thymocytes. These are exposed to major histocompatibility complexes bound to self-peptides. Those that bind with moderate affinity to self-peptides get deleted through negative selection and are selectively removed in a process known as central tolerance. Thymocytes binding with low affinity to self-antigens are positively selected and migrate to the periphery. High-affinity binding TCRs may form Treg cells, which further contribute to peripheral tolerance through prolonged interactions non-self-antigens such as food, allergens, and microbes.[1]

On a tumor cell, overexpression of self-antigens or expression of mutated self-antigens occurs, as well as expression of tumor-specific "neoantigens." In peripheral tolerance, early during the T-cell activation phase, naïve T cells express checkpoint molecule (CTLA-4) which binds to antigen presenting cells through costimulatory B7 (Figure 1). This results in an inhibitory signal, preventing response to self-antigens. Checkpoint inhibition involving blocking of CTLA-4 can result in enhancement of costimulatory signal, response to overexpressed and tumor antigens and Treg proliferation.[1]

PD-1 is another immune checkpoint, operating in the periphery that is a target of monoclonal antibodies Figure 1 that are used to treat various cancers. Anti-PD-1 therapy involves blocking the interaction of PD-1 with its ligands PD-L1 and PD-L2 and removes suppression on T cells, enhancing their proliferation.[1]

Thus, both CTLA-4 and PD-1 immune checkpoint pathways regulate activation of T cells and play a key role in preventing autoimmunity. CTLA-4 deficient mice develop spontaneous autoimmune disease in which pronounced proliferation, infiltration, and death within weeks are observed.

The irAEs can potentially arise from cross-reactivity of therapeutic monoclonal antibodies to other epitopes (molecular mimicry), or to CTLA-4 and PD-1 that are expressed in other tissues (ectopic). For example, CTLA-4 is ectopically expressed in the pituitary and cross-reactivity to this could be the cause of unintended consequences like hypophysitis from anti-CTLA-4 therapy. Self-reactive/cross-reactive TCRs combined with aberration in the costimulatory pathways might lead to alteration in the activation threshold of T cells, and change in the functional outcome. The delayed onset and long-lasting autoimmunity observed often in cases such as Type 1 diabetes appearing long after CTLA-4 blockade might be attributable to a subset of CD28- T cells. These T cells lack CD28 and have been observed to be more frequent in multiple sclerosis and other autoimmune conditions. Thus, self-reactive CD28- T cells, in which CTLA-4 has also been blocked pharmacologically, might not be disinhibited immediately, but rather behave more like memory cells that proliferate and promote inflammation at a later time.

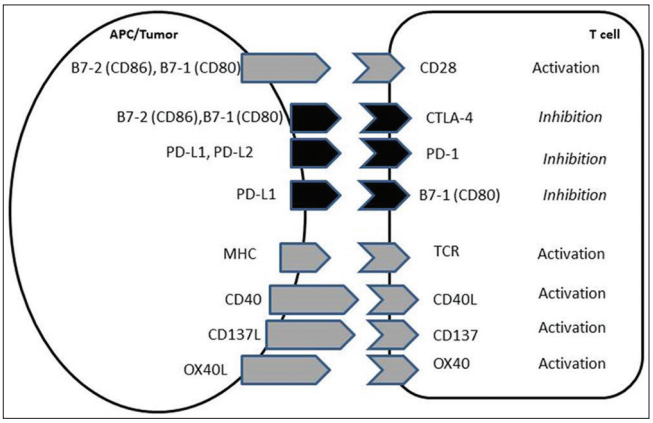

Figure 1: The interactions between cell surface receptors and ligands on the antigen-presenting cell/tumor cell and T cell leading to either activation or inhibition of the T cell

Hypophysitis

This will present with fatigue and headache which are ubiquitous symptoms for a patient on cancer therapy and likely to be dismissed as primary disease or depression. Diplopia and vertigo are other early symptoms. The CTLA-4 mechanism is thought to produce hypophysitis in approximately 3% of patients. Actual incidence is likely to be higher as it is most likely to be missed when subtle. Thyroid and adrenal failure were noted, of which thyroid failure was reversible but not adrenal insufficiency.[2] Besides, standard workup of pituitary hypofunction, magnetic resonance imaging (MRI) of skull is needed for diagnosis of hypophysitis and it is not always easy, unless radiologists are instructed that one was looking for swollen pituitary and not just CNS metastasis![3]

This probably is a scenario of underdiagnosis, and patients were followed for 6 months after the trial and not beyond and those transitioned to hospice or palliative care not further worked up.

Thyroid Disease

Hypothyroidism has been known sequelae of immune therapies since the days of using interferon. PD-1 inhibitors are known to cause thyroid hypofunction by causing primary thyroid failure (Uncanny resemblance to Hashimoto's thyroiditis).[4]

Few cases of hyperthyroidism have also been reported.[5]

Diarrhea/Colitis

Diarrhea is increased stool frequency over baseline, and colitis involves symptoms of abdominal pain, blood in stool, and either clinical or radiologic evidence of colonic inflammation.[6] The incidence of diarrhea is more common with anti-CTLA-4 mAb with any grade diarrhea occurring approximately in 30% of patients and 5–8% have Grade 3–4 diarrhea or colitis and incidence of 1–3% with anti-PD-1/PD-L1 mAb alone.[7-10] Diarrhea/colitis with anti-CTLA-4 mAb occurs within days to weeks most often after the second dose.[11] In the first phase III study of ipilimumab, five of seven deaths were caused by autoimmune colitis. Since then, with better understanding of colitis recognition and management, there have been no colitis-related deaths in recent studies.[12,13] Immune-mediated colitis commonly affects the descending colon, although imaging and endoscopy suggest that the entire colon might be affected. Upper GI tract is affected uncommonly. Pathologic features of anti-CTLA-4 mAb-related colitis include neutrophilic and lymphocytic infiltrates, and in some cases, neutrophilic cryptitis, crypt abscess, and granuloma. Prophylactic budesonide in patients with melanoma treated with ipilimumab failed to show reduction in incidence of diarrhea. However, it can provide symptomatic relief in mild diarrhea. Patient education is

important as it will ensure all diarrhea is reported and allow one to intervene early, as colitis-related mortality is increased with delayed reporting, non-compliance with antidiarrheal regimen, and failure to withhold drug. Mild or Grade 1 colitis can be managed with antidiarrheal medication like loperamide. In case of worsening or persistent diarrhea lasting for more than 3 days, it is essential to rule out an infectious cause, withholding of the CTLA-4 mAb, PD-1/PD L-1 mAb, continuing antidiarrheal medication, initiating oral corticosteroids, in addition endoscopic or radiologic evaluation should be carried out to confirm diagnosis. In clinically severe cases as Grade 3–4 or in cases that do not respond to above intervention, patients may need hospitalization for high-dose intravenous corticosteroids, for example, methylprednisolone 1–2 mg/kg total daily dose. Symptoms are expected to improve within 1–2 weeks. Once the symptoms improve, corticosteroids should be tapered slowly over at least 4 weeks for healing to complete. In case, there is no response on high-dose corticosteroids, additional immunosuppression with anti-TNF medicines such as infliximab may be indicated at a dose of 5 mg/kg. Infliximab should be administered to patients whose colitis fails to resolve within 3 days of intravenous corticosteroids or to those who had relapse of colitis with corticosteroid taper. Response to infliximab is to be expected in 1–3 days. If there is no response, patient requires a second dose. Infliximab should not be used if there is concern for perforation or sepsis.

Pneumonitis

Immune-related pneumonitis is inflammation of the lung parenchyma. Patients with suspected pneumonitis may present with shortness of breath, new or worsening cough, fever, or chest pain. The appearance of new respiratory symptoms should alert physicians to this severe and life-threatening condition.

Immune-mediated pneumonitis including sarcoidosis, and organizing inflammatory pneumonitis is rare, occurring in <10% of patients.[14] It occurs more commonly with PD-1/PDL-1 blockers than anti-CTLA-4 mAb.[15] Studies have shown that pneumonitis is more common with PD inhibitors in lung cancer patients. Pneumonitis is uncommon in melanoma using PD inhibitors, occurring in <5% on PD blockers. The incidence of pneumonitis is shown to be increased in studies where anti-PD-1/PD-L1 and CTLA-4 blockers are used in combination.[16-19] In phase III CheckMate 067 study, dyspnea was reported in 4% of patients, in both nivolumab and ipilimumab and in 11% when used in combination. In suspected cases of pneumonitis, CT scan is useful. Radiologic findings of immune-related pneumonitis show ground-glass opacities and nodular infiltrates, predominantly in lower lobes. In cases of Grade 2 or higher pneumonitis, consultation from infectious disease and pulmonary physician can be sought, to rule out overt infection and as well as lung function testing and bronchoscopy. Management is guided by clinical symptoms, mild cases can be managed by withholding therapy, and higher grade cases require treatment with oral or intravenous corticosteroids. In severe cases, hospitalization is required for intravenous corticosteroids. Antibiotics and additional immunosuppression with infliximab may be used if the severity of symptoms is not reduced.

Miscellaneous

It is scary and fascinating to look at myriad other side effects. It is fortunate that they are rare.

For example, skin rash is a known concomitant of many targeted therapies but vitiligo developing in CTLA-4 inhibitor therapy has been unnerving and may possibly unlock doors to long speculated etiologies. Pruritus is common.

Immune hepatitis needs to be watched for and may follow as late sequelae in 3–13% (in CTLA-4 Plus PD-1 inhibitor combined therapy) and may appear after some time (up to 11 months). If liver biopsy is performed, it will typically reveal diffuse T cell infiltrates.[1]

Neurological syndromes such as peripheral neuropathy, spinal demyelination, and myasthenia gravis have been described.[3]

Lymphadenopathy appearing in the middle of a cancer treatment usually leads to conclusions of cancer progression and treatment failure, but a sarcoid-like syndrome with significant adenopathy has been described.[4] Although rare (11 cases), it is probably underdiagnosed. Immune lymphocytic myocarditis is increasingly being reported as are arthritis and pancreatitis.

Type 1 diabetes mellitus in adults on immunotherapy has been reported. This is a stunning development as it may elucidate etiology and possible correction of juvenile diabetes. Reversal of Type 1 diabetes in mice using this concept has been described. Induction of PD-L1 expression on stem cells reversed diabetes in non-obese diabetic mice *in vivo* and inhibited human autoimmune responses *in vitro*.[20]

Radiologist's Challenge

Distinguishing between cancer progression and immune side effects has proven to be a learning curve. Pneumonitis, lymphadenopathy, hypophysitis, and colitis are major issues that can appear like progression and reporting needs to be cognizant of medical and legal consequences. When CT scan or MRI of head is ordered for headaches in lung cancer, it is presumed that one is looking for metastasis and swelling. Hypophysitis can be missed. It behooves treating doctors to alert radiologists of immune therapies and radiologists to bone up on the brave new world of immune consequences.[3]

Conclusions

It is imperative that knowledge about myriad disorders resulting from immune therapies become a part of education for general internists, endocrinologists, emergency physicians,

pulmonologists, and critical care personnel, as most of these will be seen and will have to be recognized in offices and settings far, far away from the domain of an oncologist. We have focused on CTLA-4 and PD-1 inhibitors that singularly and in combination have major antitumor effects, and by the same token, unleash powerful autoimmune forces. Fortunately, this is not common (10%), but for the same reason of uncommonality and ubiquitousness, it is likely to be missed.

References

1. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? Nat Med 2017;23:540-7.
2. Brilli L, Danielli R, Ciuoli C, Calabrò L, Di Giacomo AM, Cerase A, *et al.* Prevalence of hypophysitis in a cohort of patients with metastatic melanoma and prostate cancer treated with ipilimumab. Endocrine 2017;58:535-41.
3. Sidhu P, Menzies AM, Long G, Carlino M, Lorens S, Kapoor R. Radiological manifestations of immune-related adverse effects observed in patients with melanoma undergoing immunotherapy. J Med Imaging Radiat Oncol 2017;61:759-66.
4. Suozzi KC, Stahl M, Ko CJ, Chiang A, Gettinger SN, Siegel MD, *et al.* Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. JAAD Case Rep 2016;2:264-8.
5. Chistiakov DA. Immunogenetics of hashimoto's thyroiditis. J Autoimmune Dis 2005;2:1.
6. Postow MA. Managing immune checkpoint–blocking antibody side effects. Am Soc Clin Oncol Educ Book 2015;35:76-83.
7. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32.
8. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, *et al*. Nivolumab versus docetaxel in advanced squamous cell non–small cell lung cancer. N Engl J Med 2015;373:123-35.
9. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013;369:134-44.
10. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, *et al*. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): A randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908-18.
11. Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol 2006;24:2283-9.
12. Merrill SP, Reynolds P, Kalra A, Biehl J, Vandivier RW, Mueller SW, *et al.* Early administration of infliximab for severe ipilimumab-related diarrhea in a critically ill patient. Ann Pharmacother 2014;48:806-10.
13. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, *et al.* A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 2009;15:5591-8.
14. Berthod G, Lazor R, Letovanec I, Romano E, Noirez L, Mazza Stalder J, *et al.* Pulmonary sarcoid-like granulomatosis induced by ipilimumab. J Clin Oncol 2012;30:e156-9.
15. Barjaktarevic IZ, Qadir N, Suri A, Santamauro JT, Stover D. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. Chest 2013;143:858-61.
16. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS, MDX010-20 Investigators. *et al.* Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119:1675-82.
17. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, *et al.* Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32.
18. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, *et al*. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Eng J Med 2015;372:2006-17.
19. Nishino M, Sholl LM, Hodi FS. Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 2015;373:288-90.
20. Nasr MB, Tezza S, D'Addio F, Mameli C, Usuelli V, Maestro A. PD-L1 genetic overexpression or pharmacological restoration in hematopoietic stem and progenitor cells reverses autoimmune diabetes. Sci Trans Med 2017;9:7543.

How to cite this article: Vaishnav R, Arslan W, Mehta DG. Unforeseen consequences of cancer immunotherapy. Int J Mol ImmunoOncol 2018;3:20-23.

Source of Support: Nil. **Conflict of Interest:** None declared.