The dark side of immunotherapy

Nwanneka Okwundu[1], Douglas Grossman[1,2], Siwen Hu-Lieskovan[1,3], Kenneth F. Grossmann[1,3], Umang Swami[1,3]^

[1]Huntsman Cancer Institute, University of Utah Health Sciences Center, Salt Lake City, UT, USA; [2]Department of Dermatology, University of Utah Health Sciences Center, Salt Lake City, UT, USA; [3]Department of Medicine, University of Utah Health Sciences Center, Salt Lake City, UT, USA

Contributions: (I) Conception and design: U Swami; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: N Okwundu, U Swami; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Umang Swami, MD, MS. Assistant Professor, Huntsman Cancer Institute, University of Utah (NCI-CCC), 2000 Circle of Hope Drive Research North Bldg Suite No. 2121, Salt Lake City, UT 84112, USA. Email: umang.swami@hci.utah.edu.

Abstract: Immunotherapy has broadened the therapeutic scope and response for many cancer patients with drugs that are generally of higher efficacy and less toxicity than prior therapies. Multiple classes of immunotherapies such as targeted antibodies and immune checkpoint inhibitors (ICI), cell-based immunotherapies, immunomodulators, vaccines, and oncolytic viruses have been developed to help the immune system target and destroy malignant tumors. ICI targeting programmed cell death protein-1 (PD-1) or its ligand (PD-L1) are among the most effective immunotherapy agents and are a major focus of current investigations. They have received approval for at least 16 different tumor types as well as for unresectable or metastatic tumors with microsatellite instability-high (MSI-H) or mismatch repair deficiency or with high tumor mutational burden (defined as ≥10 mutations/megabase). However, it is important to recognize that immunotherapy may be associated with significant adverse events. To summarize these events, we conducted a PubMed and Google Scholar database search through April 2020 for manuscripts evaluating treatment-related adverse events and knowledge gaps associated with the use of immunotherapy. Reviewed topics include immune-related adverse events (irAEs), toxicities on combining immunotherapy with other agents, disease reactivation such as tuberculosis (TB) and sarcoid-like granulomatosis, tumor hyperprogression (HPD), financial toxicity, challenges in special patient populations such as solid organ transplant recipients and those with auto-immune diseases. We also reviewed reports of worse or even lethal outcomes compared to other oncologic therapies in certain scenarios and summarized biomarkers predicting adverse events.

Keywords: Immunotherapy; immune-related adverse events (irAEs); autoimmune; hyperprogression (HPD); solid organ transplant

Submitted Jun 16, 2020. Accepted for publication Oct 28, 2020.
doi: 10.21037/atm-20-4750
View this article at: http://dx.doi.org/10.21037/atm-20-4750

Introduction

Immunotherapy represents a breakthrough in oncology that has radically changed the therapeutic management of numerous cancer types. Multiple classes of agents have been developed to enhance the ability of the immune system to target and destroy malignant tumors but may also be associated with immune-related adverse events (irAEs) (1). These include immune checkpoint inhibitors (ICI), cell transfer therapies, vaccines, and immune system modulators. These agents, their mechanisms of action, and common irAEs are summarized in *Table 1*.

^ ORCID: 0000-0003-3518-0411.

Table 1 Selected approved cancer immunotherapies, mechanisms of action, and adverse effects

Therapy type	Mechanism of action	Examples	Selected adverse effects of interest	References
Immune checkpoint inhibitors (ICI)	Blocks checkpoint proteins, e.g., CTLA-4, PD-1 or PD-L1 from binding with their partner proteins thereby allowing the T-cells to kill cancer cells	CTLA-4—ipilimumab (Yervoy®)	IrAES: can affect any organ system, e.g., diarrhea, myasthenia graves, colitis hypophysitis, pruritus, polyarthritis	(2,3)
		PD-1—pembrolizumab (Keytruda®), nivolumab (Opdivo®), cemiplimab (Libtayo®)		
		PD-L1—atezolizumab (Tecentriq®), durvalumab (Imfinzi®), avelumab (Bavencio®)		
T cell targeted immunotherapy	Extracted patient's T cells are multiplied *ex vivo*, enhanced and administered	CAR T-cell therapies: tisagenlecleucel (Kymriah™)	CRS, neurotoxicity (e.g., convulsions, encephalopathy, or ischemia)	(4)
	These T-cells' are better able to attack and kill cancer cells	Axicabtagene ciloleucel (Yescarta™)		
	There are two main types of T-cell targeted therapy: tumor-infiltrating lymphocytes (TIL) therapy and CAR T-cell therapy			
Other monoclonal antibodies	*Ex vivo* generated monoclonal antibodies or immune system target-specific proteins are administered	CD25-specific antibody (daclizumab)	Hepatotoxicity, diarrhea	(5,6)
	These antibodies help the immune system better recognize cancer cells for destruction along with other drug specific mechanisms	CD20-specific antibody (rituximab)	CRS, immunodeficiency	
		HER2-specific antibody (trastuzumab)	Cardiotoxicity	
		CD19/CD3 specific antibodies (blinatumomab)	CRS, neurotoxicity (e.g., convulsions), liver toxicity (transaminitis)	
Anti-tumor vaccines and oncolytic virus therapy	Tumor-associated antigens (found mainly in cancer cells, but are absent or at lower levels in normal cells) are administered	Sipuleucel-T (Provenge®)	Flu-like symptoms, potential for autoimmunity	(7-9)
	The immune system recognizes and reacts to these antigens and destroy cancer cells that contain them as well as boosts T-cell or innate immune-cell responses	Oncolytic virus therapy: talimogene laherparepvec (T-VEC, or Imlygic®)		
	In oncolytic virus therapy a genetically modified virus infects and kills the cancer cells but does no or minimal harm to normal cells			

Table 1 (*continued*)

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Therapy type	Mechanism of action	Examples	Selected adverse effects of interest	References
Immunomodulators	Immune-modulating agents such as cytokines and BCG are administered	Thalidomide (Thalomid®)	Teratogenic, myelosuppression	(9-11)
	They enhance the body's immune response against cancer or reduce side effect of chemotherapy	Lenalidomide (Revlimid®)	Neutropenia, diarrhea, anemia, TLS	
		Pomalidomide (Pomalyst®)	Thromboembolism, neurotoxicity, TLS	
		Imiquimod (Aldara®, Zyclara®)	Dermatitis, cold sores, headache, flu-like symptoms	
		BCG vaccine	Hepatitis and/or pneumonitis; renal or disseminated BCG infection	
Cellular immunotherapy	Autologous or allogeneic stem cells are infused	Peripheral blood stem cells (PBSCs)	Autoimmunity due to off-target responses, including uveitis (in melanoma) and GVHD (in haematopoietic malignancies)	(9,12)
	Treat hematopoietic malignancies or aid recovery in cancer patients immunoablated with very high doses of radiation therapy, chemotherapy, or both			

BCG, *Mycobacterium bovis* bacillus Calmette-Guérin; CTLA4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; CAR T-cell, chimeric antigen receptor T-cell; HER2, human epidermal growth-factor receptor 2; irAEs, immune-related adverse events; TLS, tumor lysis syndrome; CRS, cytokine release syndrome; GVHD, graft versus host disease.

Immunotherapies have improved overall survival (OS) in a broad range of early-stage and advanced cancer types, and these treatments have gained wide acceptance and considerable excitement in clinical practice. Antibodies targeting programmed cell death protein-1 (PD-1) or its ligand (PD-L1) are the most effective of the ICIs. As per a recent report, at least nine PD-1/PD-L1-directed agents have reached the clinics globally for the treatment of 16 different cancer types, and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors (13).

However, these novel agents are not without their unique downsides which include high cost, immune toxicities, hyperprogression (HPD), reactivation of certain diseases, limitations in certain populations, and unexpected worse outcomes in certain malignancies. This review summarizes these negative health impacts and problems associated with the use of immunotherapy (*Figure 1*).

irAEs

Although immunotherapy has proven to be more effective and less toxic compared to chemotherapy in multiple cancer types, unexpected adverse events have been observed that are likely related to their mechanism of action (14). These therapies generally work by relieving inhibition of activated T-lymphocytes in lymph nodes and peripheral tissues, resulting in enhanced lymphocyte activation and propagation of T-cell mediated destruction of normal cells expressing self-antigens and induce inflammatory and auto-immune responses leading to irAEs (6). Clinically, irAEs may manifest as distinct symptoms with respect to organ

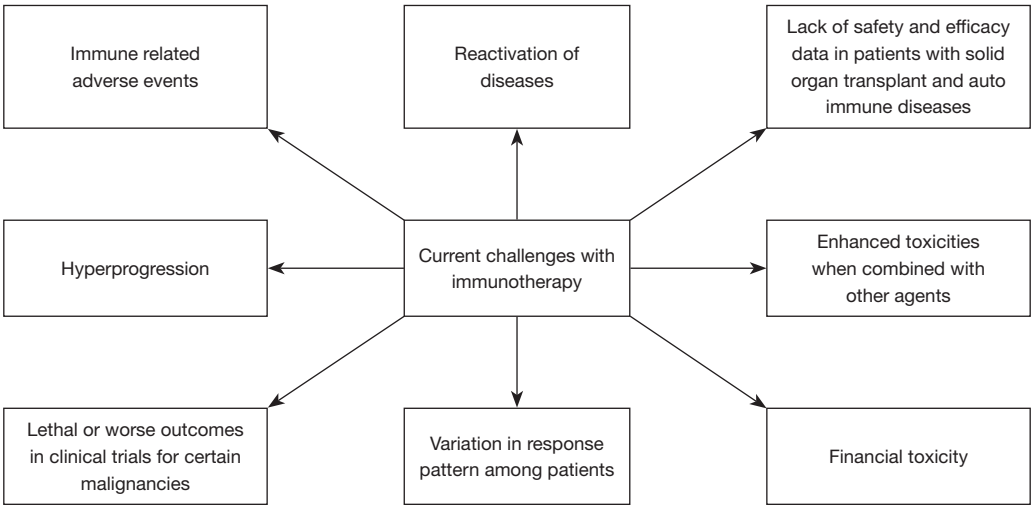

Figure 1 Summary of current challenges with cancer immunotherapy.

involvement, pattern of onset, and level of severity which may lead to severe and even life-threatening complications in patients that may necessitate early termination of an otherwise beneficial treatment. Up to 95% of patients receiving immunotherapy may experience irAEs (15-19) mainly due to immune dysregulation targeting normal tissue antigens (20-22). In initial reports, the organs most frequently involved were the skin (pruritus and cutaneous rash), joints, thyroid, and gastrointestinal tract (colitis and diarrhea). Subsequently, irAEs were identified in the liver (autoimmune hepatitis), non-thyroid endocrine glands (hypophysitis and adrenal insufficiency), lungs and nervous system (myasthenia gravis and encephalitis). Finally, myositis/myocarditis, nephritis, and even hematological irAEs were reported (23–25). Interestingly, irAEs may be idiosyncratic as different drugs and doses used for different cancers may result in different adverse events of unpredictable severity (23,26,27).

The irAEs induced by ICI therapy are associated with a fatality rate of around 5%. In an analysis of co-morbidities in 21 patients on ICI with irAEs related death, 12 had hypertension and 6 had other cardiac conditions; 2 patients had a preexisting autoimmune disease (AD) (Graves' disease). In addition, patients with fatal toxic effects had similar sex distribution but were older than those without fatal toxic effects (median, 70 *vs.* 62 years; absolute difference, 8; P=0.009) (28). The most common cause of death from ICI-related irAEs is (ICI)-related pneumonitis (ICI-P). The incidence of ICI-P in phase III trials was between <0.5% and 10% for all grades and has been found to be higher in lung cancer (1–6%) than in other cancers (0.1–4%) (29–37). In a meta-analysis including all cancer types and ICI, ICI-P of all grades was observed in 2.6% of patients and emerged as the fourth leading cause of ICI-induced irAEs after skin eruptions (13.9%), hepatitis (6.5%), thyroid disorders (5.1%), and colitis (2.3%) (38). In another meta-analysis, the most common irAEs due to PD-1 and PD-L1 inhibitors were fatigue (18.3%), pruritus (10.6%), and diarrhea (9.5%). Though the incidence of all grade ICI-P was 2.79% it was responsible for 28% of treatment-related deaths (39).

Immune-mediated myocarditis is the most common type of cardiotoxicity occurring with immunotherapy. Although the incidence is low partly due to under-recognition, the cardiovascular-specific mortality rate is relatively high and varies with different therapies. In patients who developed cardiotoxicity, the cardiovascular-specific mortality was 12% in patients receiving nivolumab monotherapy, 19% in pembrolizumab monotherapy cohorts, and 65% in combined CTLA-4 and PD-1 blockade (ipilimumab and nivolumab combination) (40).

Endocrine adverse events though rare could be life-threatening and hence are noteworthy irAEs. Blocking inhibitory molecules on activated T cells by ICI not only increases the killing of tumor cells it could also lead to infringement of self-tolerance, enabling T cells to act against self-antigens (41). The most frequent autoimmune endocrinopathies involve the pituitary and thyroid

glands (42). Thyroid abnormalities such as hypothyroidism, thyrotoxicosis, painless thyroiditis, or even thyroid storm (43) are present in 1–6% of patients administered with ICI (43,44). Patients with endocrine irAE can be critically ill at presentation. For instance, primary adrenal insufficiency during immunotherapy is a medical emergency requiring hydrocortisone replacement. Suggestive acute symptoms include hypotension, hyponatremia, nausea, vomiting, diarrhea, asthenia, weight loss, dehydration, fever, abdominal pain, cramp and muscle pain. Current data suggest that treatment needs to be life-long, even after termination of immunotherapy (45).

Furthermore, patients could develop autoimmune type 1 diabetes and also often present emergently with severe hyperglycemia or diabetic ketoacidosis (DKA) with elevated HbA_{1c}. Time from drug administration to diabetes onset may span 1 week to 5 months (41). In a systematic review of 90 patient cases treated with anti-PD-1 or anti-PD-L1 as monotherapy (79%) or in combination with CTLA-4 blockade (15%), diabetes mellitus was diagnosed after 4.5 cycles (range, 1–17); while earlier with combination ICI at 2.7 cycles (range, 1–5) on average. Islet autoantibodies were positive in 53% (47/88) of patients with a predominance of glutamic acid decarboxylase antibodies. Susceptible HLA genotypes were present in 65% (mostly DR4) (46). Hence, the use of anti-GAD serology in aiding the diagnosis is not recommended as only half of the patients were positive although this can potentially be used to confirm the diagnosis if positive (47). Incidence is estimated to be at 0.4–0.6% in clinical trials (44,48,49), while a recent study reported a prevalence of 0.9% among 2,960 patients treated by immunotherapy (50). Immune-related endocrine toxicities such as thyroid dysfunctions, hypophysitis, adrenal insufficiency, and type 1 diabetes mellitus are irreversible in approximately 50% of patients (51).

Most of the irAEs symptoms are generally well-controlled by discontinuing the drug and/or adding systemic glucocorticoids or steroid-sparing regimens (e.g., anti-tumor necrosis factor-alpha (TNF-α) agents or mycophenolate mofetil). Systemic steroids are usually administered for months and sometimes multiple courses are needed due to repeat flares of these irAEs after taper. This makes the patients immunocompromised for a prolonged period, putting them at risk of infections. In addition, corticosteroid-associated adverse events such as myopathy, gastritis, diabetes mellitus, hypertension, Cushing's syndrome and osteoporosis remain a cause of concern (52).

Biomarkers for irAEs

Certain biomarkers have been found in studies to be independently predictive of irAEs such as female sex and low baseline cytokine levels. Low IL-6 levels were associated with increased OS in a study of 140 patients with melanoma treated with anti-CTLA-4 (53). In patients with locally advanced or metastatic melanoma an association between ipilimumab-induced colitis and reduced baseline levels of circulating IL-6, IL-8, soluble IL-2 receptor (sCD25), and increased IL-17 has been demonstrated (54,55). Intriguingly, there is a likelihood that the net increase in these proinflammatory cytokines from ICI therapy actually determines immune toxicity. On therapy increases in IL-6 (56) or in soluble cluster of differentiation 163 (sCD163) (57) in two studies of melanoma cohorts treated with nivolumab monotherapy were predictive of psoriasiform dermatitis and a variety of irAEs, respectively.

In addition, the existence of autoantibodies may predict the development of endocrine-specific irAEs following checkpoint inhibition. Increased pretreatment levels of serum antithyroglobulin antibodies was significantly associated with subsequent autoimmune thyroid dysfunction (odds ratio, 26.5; 95% CI, 8.18–85.8) in a multivariate analysis of patients with advanced solid tumors treated with nivolumab (58). Another study found that the existence of one or more diabetes autoantibodies (against glutamic acid decarboxylase 65, insulin, islet cells, zinc transporter 8, or islet antigen 2) prior to ICI therapy precipitated the development of clinical diabetes in a cohort of patients diagnosed with a variety of solid tumors (50). Moreover, proteome array identified baseline serum antibody reactivity in a study of 78 patients treated with ICIs. Machine learning has also identified baseline antibody signatures associated with irAEs with greater than 90% sensitivity and specificity (59).

Furthermore, the constitution of the gut microbiota may be associated with ICI-induced colitis. For instance, in a prospective study of 34 patients with melanoma treated with anti-CTLA-4, baseline representation of species from the Bacteroidetes phylum was associated with decreased risk of ICI-induced colitis (60). Consequently, some studies have reported a positive association between the on-therapy incidence of irAEs and OS or response for patients treated with anti-CTLA4 (61) or anti-programmed cell death 1 (PD1) (62-64), while others found no association with OS (65,66).

Reactivation of diseases

Immunotherapeutic agents may also unmask chronic underlying diseases or opportunistic infections. These include latent tuberculosis (TB), sarcoid granulomatosis, varicella-zoster virus infection, cytomegalovirus-associated enterocolitis, and their potentially serious complications which compromise treatment outcome and patient survival (67,68). In an analysis of 14 cancer patients with active TB infection following PD-1/PD-L1 blockade, only 2 of 14 (14%) patients who developed active TB infection had received steroids or infliximab for irAEs. Thus, cancer and/or the immunotherapeutic drugs could be considered the probable etiology of their susceptibility to the TB infection warranting caution (69-77). Hence, in addition to high-dose corticosteroids, which when used to manage irAEs can unmask chronic underlying diseases or opportunistic infections, immunotherapeutic drugs could directly reactivate diseases as well.

This direct complication of immunotherapy correlates with the findings in a study which investigated the expression patterns of PD-1 and PD-L-1 within TB-infected human lung tissue using a human 3D cell culture model of TB. It was found that PD-1 regulates the immune response in TB (78), and that inhibition of PD-1 accelerates TB bacteria growth through excessive TNF-α secretion (79). Neutralizing TNF-α reversed the augmented growth caused by PD-1-inhbitor therapy (79). This is also the basis for treatment of irAEs associated with ICIs with anti-TNF-α inhibitors (1), suggesting TNF-α may be responsible for both autoimmunity and TB pathology after PD-1 therapy.

Some cancer types and immunotherapeutic drugs have been associated with certain disease reactivation susceptibility. For instance, reactivation of sarcoid-like granulomatosis is associated with ICI treatment for melanoma. Of 19 isolated cases of immunotherapy-related sarcoid-like granulomatosis (ICI-SLG) reported after initiation of cancer treatment, (80-95), 13 (73%) were melanoma patients. Similarly, ICI-SLG occurred in 7 out of 509 (1.4%) stage 3 melanoma patients treated with pembrolizumab, while no ICI-SLG occurred in the placebo group (96). It was also found that melanoma was the most common cancer type associated with sarcoidosis in a meta-analysis investigating the association between sarcoidosis and cancer, and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors also had a higher association with ICI-SLG than PD-1 inhibitors (97). Sarcoid presents a particular problem as it is often mistaken for cancer on scans as a sarcoid flare can be hard to distinguish from progressive disease.

Patients with transplant and auto immune diseases

Safety and efficacy data are lacking for the use of immunotherapy in patients who have undergone solid organ transplantation (SOT). As a result, these patients have been excluded from clinical trials (20,98,99). There is a concern for the risk of allograft rejection in SOT patients (98). In addition, the immunosuppressive drugs used to manage SOT patients may decrease the immune enhancement and efficacy of immunotherapy (99). In a systematic review of SOT patients treated with ICI, allograft rejection occurred in 37% and 14% died as a result of graft rejection. Nivolumab was associated with rejection in about half of patients, while pembrolizumab and ipilimumab were each associated with rejection in about one quarter of patients. Highest rates of graft rejection were seen with kidney (40%), followed by liver (35%), and heart (20%) (100). Graft rejection can be reversed in some patients with the use of high-dose corticosteroids, and occasionally other aggressive immunosuppressive therapies, along with dialysis and ICI discontinuation (101). Furthermore, SOT patients are at increased risk of developing *de novo* cancers (102-106) which are the second leading cause of death in this patient population (106). The inability to safely use immunotherapy without risk of allograft rejection in these patients poses a significant therapeutic challenge.

In addition, disease exacerbation as well as more severe irAEs may occur in patients with active AD treated with immunotherapy (98). Immune enhancement by immunotherapy may also exacerbate preexisting AD in remission. In a systematic review which assessed the use of immunotherapy in the treatment of 123 cancer patients with preexisting AD, 75% reported adverse events and 41% experienced exacerbation of the preexisting AD with recurrence manifestation or worsening of prior symptoms (101). Flares were more common in patients with active symptoms (9/15, 60%) as compared to those with subclinical disease (11/37, 30%). Overall, 50% had disease exacerbation, and 34% had *de novo* irAEs. Colitis (14%) and hypophysitis (5%) were the most commonly reported *de novo* irAEs. Therefore, patients with active AD were usually excluded from clinical trials. Now

multiple clinical trials (107,108) are evaluating ICI in patients with AD.

Potential strategies beyond clinical guidelines have been proposed to lower the risk of irAEs for these specific scenarios. These include use of specific selective systemic immunosuppressant instead of nonselective immunosuppressant drugs (98), discontinuation of the immunotherapeutic drug followed by a rechallenge with the same drug (109) or rechallenge with PD-L1 inhibitors after intolerable irAEs with anti PD-1 agents (110). In a comprehensive retrospective study of patients treated with ICI, 28.8% of 24,079 irAE cases represented recurrence of the same irAE after discontinuation and rechallenge with the same ICI. Colitis, hepatitis, and pneumonitis were associated with a higher recurrence rate, while adrenal events were associated with a lower recurrence rate (109). However, none of these strategies have been rigorously tested in patients with SOT and AD.

Enhanced toxicities when combined with other agents

Combination of immunotherapy with other agents may enhance efficacy but toxicity is also increased (111). Immunotherapy can be combined effectively with other immunotherapeutic drugs, chemotherapy, targeted therapy, and radiotherapy (25). The use of immunotherapy as a single agent may be constrained by the several factors existing in the tumor microenvironment, such as insufficient T cells from the naive repertoire, inadequate available neoantigen, or immunosuppressive networks which protects the immunogenic tissue from immune attacks. Combining cancer therapies could strengthen the immune response by inducing immunogenicity, alleviating tumor-induced immunosuppression associated with chemotherapy, or rendering tumors more susceptible to cytotoxic T cell attack (111). In patients with melanoma, five-year OS with combination of ipilimumab with nivolumab was 52% as compared to 44% with single agent nivolumab. However, combination treatment also resulted in a higher grade 3/4 treatment related adverse events (59% *vs.* 23%) (112). It is also unknown whether treatment with a PD-1 inhibitor first, followed by treating patients at progression with nivolumab/ipilimumab, can achieve the same OS with less toxicities.

While several combinations of BRAF and MEK inhibitors (BRAF/MEKi) and immunotherapy (mainly anti CTLA-4 and anti PD-1 therapies) increased OS in melanoma patients (113), phase I trials of BRAF/MEKi with ipilimumab were halted due to unacceptable toxicities. A trial investigating the combination of BRAF inhibitor, vemurafenib plus ipilimumab was halted due to hepatotoxicity (114). The combination of dabrafenib, trametinib, and ipilimumab led to colon perforation in two of the seven patients treated in the phase I trial, while excluding trametinib resulted in no such toxicity (115). In a case report of a melanoma patient treated with sequential BRAF/MEKi (dabrafenib plus trametinib) followed by the ipilimumab, the patient had a complete resolution of the tumor, but died due to fatal gastrointestinal toxicity (113). Contemporary data sets of triplet therapy now show better safety of PD-1 inhibitor combined with BRAF/MEKi (116).

The efficacy and toxicity of immunotherapy combined with other therapies depends on the drug, and relative timing of the combination (117). The critical challenges associated with combining cancer therapy are incorporating immunotherapy into adjuvant and neoadjuvant treatments, determining the accurate dose, duration of treatment, selecting appropriate biomarkers, and designing new surrogate endpoints that accurately define OS benefit at treatment initiation (25). Finally, early identification and treatment of myelosuppression and irAEs associated with disease management with chemo-immunotherapy are necessary, as early treatment enhances survival (111).

HPD

Despite the success of cancer immunotherapy in demonstrating efficacy across multiple cancer types, it has also been implicated in accelerating disease progression, a concept known as HPD. Notably, this is not as common with other cancer therapeutics (118,119). In a multicenter, retrospective study comparing the incidence of HPD in lung cancer patients receiving ICI therapy versus chemotherapy, HPD occurred in 14% of patients treated with immunotherapy (N=406), compared to 5% of patients receiving chemotherapy (N=59) (120). The rate of ICI-associated HPD was as high as 10–30% in retrospective studies (120-122). Variation in the incidence of HPD may result from lack of a unified definition for HPD including or not accounting for non-target lesions like malignant effusions, bone metastases, or new disease sites. Many of the studies were tumor type-specific, and lack of baseline imaging excluded many patients from analysis (118,123). In

addition, some patients did not meet radiological criteria for HPD because they experienced rapid clinical deterioration with immunotherapy and could not be evaluated by CT scan (120,121).

Understanding and assessing HPD is further complicated by a phenomenon called pseudoprogression, which refers to transient radiographic worsening (enlarging and/or new tumor lesions) prior to a regression or successful treatment response. This is thought to stem from an early influx of tumor-infiltrating lymphocytes propagating an early but temporary increase in tumor dimensions (124-126). The crucial challenge for oncologists is to distinguish pseudoprogression (affecting less than 10% of patients (126-128) from standard progression and HPD as this frequently leads to unnecessary discontinuation of a beneficial treatment.

Clinical studies aimed at making this distinction have found HPD to be associated with increased age (121), mutations in a variety of oncogenes (129), higher lactate dehydrogenase (LDH) concentration in the serum (122), female sex (130), prior irradiation of the tumor area (131), presence of liver metastasis or more than two metastatic sites (132), MDM2/MDM4 and EGFR genetic alterations (133,134). However, most study results were not replicated by other studies (135). There is an urgent need for a consensus on a unified definition of HPD so that studies across tumor types can be compared or pooled to achieve a higher statistical power (118).

Lethal or worse outcomes

Although generally rare with PD-1 inhibitors, some immunotherapeutics resulted in worse and even fatal outcomes in some clinical trials for hematologic malignancies. One example is the chimeric antigen receptor (CAR) T-cell therapy, which is Food and Drug Association (FDA)-approved for refractory or relapse (R/R) B cell precursor acute lymphoblastic leukemia (ALL) in pediatric patients and young adults and for R/R large B cell lymphoma in adults. Despite a 92% response rate in ALL (136,137), in 2016, 5 adult ALL patients died while receiving JCAR015 CAR T-cell therapy. In 2017, a death also resulted in a patient who received UCART123 CAR T-cell therapy during a phase I trial for leukemia. These deaths were associated with the development of neurotoxicity/cerebral edema and cytokine release syndrome (CRS) (138). CRS is an extreme systemic inflammatory response that can progress to sepsis and multiple organ failure (139). Furthermore, in 2017, the FDA halted two KEYNOTE phase III trials involving pembrolizumab in patients with multiple myeloma due to disproportionately higher deaths in the treatment group compared to controls (138).

The KEYNOTE-183 phase III trial studied pembrolizumab in combination with pomalidomide and low-dose dexamethasone in 249 patients with relapsed/refractory multiple myeloma. Twenty-nine (23%) deaths (16 from progressive disease and 13 from adverse events) occurred in the triple therapy group, compared with 21 (17%) deaths (18 from progressive disease and 3 from adverse events) in the pomalidomide with dexamethasone control group (138,140). The KEYNOTE-185 phase III studied pembrolizumab in combination with lenalidomide and low-dose dexamethasone for newly diagnosed treatment naive multiple myeloma. Nineteen (13%) (6 because of disease progression and 13 because of adverse events) deaths occurred with triple therapy, compared with 9 (6%) deaths (one because of disease progression and 8 because of adverse events) in the group receiving only lenalidomide and dexamethasone (138,141).

Treatment-related deaths during these trials were attributed to serious adverse effects such as cardiac arrest and failure, large intestine perforation, sepsis, multiple organ failure, Stevens-Johnson syndrome, pulmonary embolism, and respiratory tract infections (138,140). It is not clear if the deaths resulted from the interaction of PD-1 inhibitor with pomalidomide or lenalidomide, or with other concurrent medications.

Variation in response pattern among patients

Nivolumab has demonstrated activity and favorable safety profile in pediatric patients with glioblastoma in a Phase III clinical trial (CheckMate-143) (142). All adverse events in the 10 nivolumab-treated patients were grade 1 or 2, with fatigue and nausea as the most common adverse events (143). Despite these safety data, a pediatric patient with glioblastoma treated with nivolumab died from progressive cerebral edema after third treatment (142). By contrast, two pediatric patients with glioblastoma treated with nivolumab experienced transient cerebral edema that subsided with repeated doses and addition of dexamethasone (142,144). Another example of variable patient response includes nivolumab for adult T-cell leukemia-lymphoma (ATLL) in which some patients experienced rapid progression while most did not (145,146). Different disease variants may have accounted for the disparate responses.

Analysis of three patients who experienced rapid ATLL expansion after PD-1 blockade demonstrated association with tumor-resident regulatory T cells (Tregs), independent of the unique subtype of the atypical cell present in each patient (147). More studies are clearly needed to understand the variation in patients' adverse responses to immunotherapy.

Financial toxicity

The cost of immunotherapy is approximately $100,000 per patient annually (148). This amount exceeds the median U.S. household income and recently FDA-approved immunotherapeutic drugs are often triple the cost of drugs approved in previous years (149). For instance, the CAR T cell therapy Tisagenlecleucel which was FDA-approved for treatment of R/R B-cell ALL in patients ≤25 years old, is associated with improved OS but costs $475,000 per treatment course, not including cost of hospital stay and toxicities. Its manufacturer, Novartis, is offering a money back guarantee for patients who do not achieve remission within one month of receiving treatment (150).

Studies suggest that some immunotherapeutic drugs were not more cost-effective than chemotherapy based on the quality-adjusted life years (QALYs) gained for some indicators. Cost-effectiveness analysis (CEA) expresses the potential value of new drugs (compared to previous treatment) per health benefits gained in terms of units of currency. The outcome considers OS and is presented as an incremental cost per QALY (151). In a systematic review of the cost and cost-effectiveness studies of ICI, nivolumab was not cost-effective over chemotherapy for recurrent/metastatic head/neck cancers (HNCs) and NSCLC. Nivolumab and pembrolizumab were not cost-effective for genitourinary cancers, while ipilimumab monotherapy is less cost-effective than nivolumab, nivolumab/ipilimumab, and pembrolizumab for melanoma (152).

Even though many of the immunotherapeutic drugs were found in analytic studies to be cost-effective, this does not necessarily translate into affordability. This has led to rejection of ICI by British National Institute of Clinical Excellence (NICE) and Australian Pharmaceutical Benefits Advisory Committee (PBAC) for some indications (153). Consequently, it is also important for CEA to be performed before FDA approval of these drugs. We also need a lasting solution to curb the current cancer cost trajectory which is untenable for most healthcare systems in the long run, and to save the numerous patients who are going into bankruptcy due to the financial burden of their cancer care (149).

Conclusions

Despite dramatic therapeutic successes, immunotherapeutic drugs can be associated with numerous and unpredictable toxicities. Furthermore, there is a knowledge gap relating to how these drugs work in different patient populations with various disease conditions. Further clinical studies are needed to maximize the benefits and minimize the risks of immunotherapy. There is also a need to address the rising costs of cancer care to relieve the negative financial burden on patients. Nonetheless, immunotherapy has undoubtedly changed the treatment landscape of oncology care giving patients a greater potential to attain long term survival, improved quality of life, and less toxic treatment options. However, prospective evidence-based studies are necessary to more accurately understand the variation in patient responses and treatment related adverse events, to obtain the full benefit of these promising new drugs.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine* for the series "Cancer Immunotherapy: Recent Advances and Challenges". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4750). The series "Cancer Immunotherapy: Recent Advances and Challenges" was commissioned by the editorial office without any funding or sponsorship. US served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Annals of Translational Medicine* from May 2019 to Apr 2021. Dr. SHL reports consulting for Amgen, Merck, Genmab, Xencor, BMS, research support from BMS, Merck, Vaccinex and contracted research from Neon Therapeutics, Astellas, F Star, Xencor, Merck, Vedanta, Boehringer Ingelheim. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Okwundu N, Grossman D, Hu-Lieskovan S, Grossmann KF, Swami U. The dark side of immunotherapy. Ann Transl Med 2021;9(12):1041. doi: 10.21037/atm-20-4750

