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Top Ten Tips for Palliative Care Clinicians Caring for Cancer Patients Receiving Immunotherapies

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Abstract

Patients with cancer face an ever-changing landscape of tumor-directed therapies available to improve quality of life and potentially increase survival. The most recent advances, immunotherapeutics, offer a novel way to target cancer cells by engaging the body's own immune system. Using an expert panel of oncologists, palliative medicine physicians, and dual-trained specialists, we discuss current immunotherapies and their clinical uses, potential side effects and management strategies, and the implications of these newer treatments on goals of care conversations and care coordination. We aim to further engage palliative care specialists in the active care of cancer patients receiving immunotherapeutics and use a ''Top 10'' tips format to concisely present practical learning points to busy clinicians.

Keywords: cancer patients; immunotherapeutics; immunotherapy; palliative care; tumor-directed therapies

Introduction

''Immunotherapeutics,'' treatments that modify a patient's own immune system for anticancer purposes, are rapidly expanding the therapeutic toolbox for oncologists, with great advances over the last five years. Immune checkpoint inhibitors are the most commonly used FDA-approved immunotherapies for several conditions, including melanoma, head and neck cancer, bladder cancer, and non-small-cell lung cancer (NSCLC), among others. Given their promise of durable remissions in some patients with metastatic cancer, immunotherapeutics represent a significant proportion of the therapeutics pipeline for pharmaceutical companies. Use of these agents is only expected to expand, both across various cancers and earlier in cancer treatment.

Using a ''Top 10'' tips format, this article seeks to introduce palliative care clinicians to these novel agents, describe current immunotherapies and their clinical uses, review potential side effects and management strategies, and discuss implications on goals of care conversations and care coordination.

Tip 1. There are several classes of immunotherapeutics; most used in routine practice today are checkpoint inhibitors

Checkpoint inhibitors are the most widely used class of immunotherapeutics in routine practice. Immune checkpoint inhibitors, sharing the suffix ''-mab'' for monoclonal antibody, block the interaction between cancer cells and the immune system. Cancer cells express proteins that suppress the immune system, and immunotherapies seek to block this ''brake,'' allowing the body's immune system to target the cancer.[1] There are currently six FDA-approved immunotherapies (Table 1). Pembrolizumab, a programmed cell death-1 (PD-1) inhibitor with activity in melanoma, gastric cancer, head and neck cancer, NSCLC, microsatellite instability-high cancer, renal cell carcinoma (RCC), and Hodgkin's Lymphoma, is now first-line treatment for NSCLC patients with greater than 50% expression of PD-1.[2,3] Nivolumab is a PD-1 inhibitor with activity in melanoma, NSCLC, head and neck cancer, colorectal cancer, RCC, and hepatocellular carcinoma. A landmark study of nivolumab

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Table 1. Immunotherapies and FDA-Approved Indications

Checkpoint	*Inhibitor*	*FDA approved tumor targets*
PD-1	Nivolumab	Melanoma, NSCLC, colorectal, head and neck, Urothelial, Hodgkin's lymphoma, RCC, HCC
	Pembrolizumab	Melanoma, NSCLC, gastric, head and neck, Urothelial, Hodgkin's lymphoma, microsatellite instability-high cancer
PD-L1	Atezolizumab	Urothelial cancer, NSCLC
	Durvalumab	Urothelial cancer
	Avelumab	Urothelial cancer, Merkel cell cancer
CTLA-4	Ipilimumab	Melanoma

CTLA-4, cytotoxic T lymphocyte–associated antigen 4; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma.

Table 2. Immunotherapy Side Effect Frequency and Treatments for Grade 3+ Toxicities

Side effect	*Frequency*	*Treatment*
Fatigue	10–40%	Exercise, stimulants, and/or supportive care
Rash/pruritis	30–50%	Topical +/− systemic glucocorticoids
Diarrhea/colitis	14–30%	Glucocorticoids, consider anti-TNF if refractory or worsening symptoms
Pyrexia	~10%	Acetaminophen, NSAIDs
Pneumonitis	<5%	Systemic glucocorticoids
Transaminitis	10–20%	Monitoring, dose modification and/or delay
Endocrinopathies:	10%	
Hypothyroidism		Thyroid hormone replacement
Hyperthyroidism		Monitoring, dose modification and/or delay
Hypophysitis		High-dose glucocorticoids, hormone supplementation
Adrenal insufficiency		Hospitalization, endocrine consult
Diabetes mellitus type 1		Insulin

NSAIDs, nonsteroidal anti-inflammatories.

plus ipilimumab (an antibody against cytotoxic T lymphocyte–associated antigen 4 [CTLA-4]) showed tumor regression of over 80% in more than half of patients with advanced melanoma.[4] Three programmed death-ligand 1 (PD-L1) inhibitors have been approved for treatment of bladder cancer: atezolizumab, durvalumab, and avelumab. Atezolizumab has also shown activity in a phase I trial in NSCLC,[5] and avelumab has activity in Merkel cell carcinoma. Multiple new therapies are coming down the pipeline, with exciting implications for other tumors.

Tip 2. Checkpoint inhibitors have unique side effect profiles compared with conventional cytotoxic chemotherapy

Side effects related to the use of immunotherapeutics are different than conventional cytotoxics and often incorrectly considered not as significant. Typical chemotherapy side effects such as hair loss and blood cell abnormalities are not prevalent with checkpoint inhibitors; major clinical trials of immunotherapeutic agents demonstrate distinct grade 3 or 4 toxicities. Immune-related adverse events (irAEs) are summarized in Table 2.

In general, for patients with grade 2 (moderate) toxicities, treatment is held and resumed when toxicity is grade 1 or less.[6] Glucocorticoids (prednisone 0.5 mg/kg/day or equivalent) are indicated if symptoms continue longer than a week after drug cessation. Specifically, for patients with grade 3 or 4 toxicities, the checkpoint inhibitor should be discontinued without retrial. High-dose glucocorticoids (prednisone 1 to 2 mg/kg/day or equivalent) are recommended for four to six weeks, followed by a slow taper after resolution or improvement of symptoms to grade 1 or less. If symptoms do not improve in the first three days, infliximab (5 mg/kg) may be tried in lieu of continued high-dose glucocorticoids.

irAEs often present in a temporally predictable way. Dermatologic side effects are often the first-noted toxicity, and colitis presents later, around six weeks into treatment. Severe colitis occurs in less than 10% of patients treated with ipilimumab, with increased risk of peritonitis or bowel perforation. For patients with more than seven times their baseline bowel movements, intravenous glucocorticoids, hydration, and hospitalization are indicated. Endocrinopathies can occur in up to 10% of patients, and treatment should be targeted at replacing/managing the affected hormone. Of note, most endocrinopathies are permanent and require lifelong replacement. Rarer irAEs include episcleritis, uveitis, pancreatitis, neuropathies, nephritis, and cardiomyopathies.

Tip 3. Glucocorticoids do not reduce the efficacy of checkpoint inhibitors, and are sometimes necessary, life-saving interventions for irAEs

Most irAEs are clinically manageable with the use of systemic glucocorticoids. Because they counteract the same immune system activated by immunotherapies to attack the cancer, some clinicians may incorrectly believe that glucocorticoids are contraindicated in combination with immunotherapy, fearing they may reduce the efficacy of immunotherapy. Thus, clinicians may be reluctant to use glucocorticoids to palliate immunotherapy side effects, given concerns that they will block their potential therapeutic effects. This has led to a dichotomous "all-or-none" approach to glucocorticoid use, which we encourage our palliative care colleagues to avoid. In fact, most clinical trials of immunotherapies allow for glucocorticoid use up to a dose of oral prednisone 10 mg daily or equivalent, concurrent with the provision of immunotherapy.

We recommend that palliative care clinicians engage their oncology colleagues in a conversation before using glucocorticoids, focusing on the *if* and *when* glucocorticoids should be used. Immune-related toxicities are common, and

approximately one-third of patients require systemic glucocorticoids. Clinicians should be prepared to treat these irAEs and understand that doing so should not affect overall survival or time to treatment failure.[7] In fact, low-dose oral glucocorticoids may be the only way for patients to continue on effective immunotherapy in the setting of low-grade irAEs. In coordination with the oncology team, when patients experience grade 2 or 3 irAEs, general recommendations as discussed above are to start oral prednisone 1 to 2 mg/kg/day or dexamethasone 4 mg every four hours, followed by a taper over the next four weeks.[8] Severe immune-related side effects (e.g., pneumonitis, colitis) may require four to six weeks of glucocorticoid treatment with a slow taper.

Tip 4. Oncologists routinely evaluate, grade, and monitor the severity of irAEs

Oncologists routinely order and monitor a core set of screening laboratory values before the administration of each cycle of immunotherapy to evaluate for irAEs. Guidelines for irAE assessment, cosponsored by the American Society of Clinical Oncology and the National Comprehensive Cancer Network, are in development,[9] but we currently lack definitive guidance regarding which laboratories to assess and at what frequency. Consequently, variation exists across clinicians and institutions. When clinical symptoms define the irAEs (e.g., pneumonitis, colitis), routine laboratory monitoring is less important; however, routine laboratory evaluation is critical with the vague clinical presentations that may constitute immune-mediated hepatitis, pancreatitis, and endocrinopathies.

Laboratory monitoring is also based on frequency and severity of irAEs. The standardized set of criteria for grading adverse events across all cancer studies is the Common Terminology Criteria for Adverse Events (CTCAE),[10] and more standardized immunotherapy-specific scales are in development (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/jpm). Laboratory evaluations are a key component of this grading system. As part of standardized electronic medical prescribing, most institutions include a set of irAE screening laboratories, including, but not limited to, complete blood count, complete metabolic profile, cortisol, thyroid stimulating hormone (TSH), free thyroxine, and either an amylase or lipase (Table 3). When symptoms occur such as fatigue, dizziness, changes in weight, visual disturbances, and abdominal pain, then these standard screening laboratories may be used to guide an appropriate clinical workup.

Tip 5. Immunotherapy adverse events and symptoms related to cancer can resemble each other; timing and severity may give a clue

With the exception of treatment of NSCLC, immunotherapies for anticancer purposes are limited to the late-line metastatic setting. Several ongoing clinical trials are evaluating the role of immunotherapies more upstream. These two populations–those with advanced disease and those undergoing clinical trials–may have several concurrent noncancer morbidities (e.g., heart failure, COPD) or acute issues related to downstream effects of previous cancer therapies (e.g., C. difficile colitis as complication of antibiotic use for neutropenic fever). A bevy of acute and chronic conditions combined with active and progressive cancer can make it difficult to ascertain a particular symptom's cause (i.e., adverse event vs. cancer-related vs. unrelated condition).

Clinical trial data demonstrate that most immunotherapy toxicities have a relatively predictable time course. Skin manifestations present earliest, sometimes only two to three weeks after initiation. More severe organ dysfunction such as immune-mediated colitis, hepatitis, and pneumonitis require more exposure to immunotherapies and time, appearing at least 5 weeks after the second dose, and usually closer to 10–12 weeks. Endocrine dysfunctions, such as those affecting the adrenal glands and thyroid, present from the second month onward, and immune-mediated pneumonitis can present 8–14 weeks after treatment initiation.[11,12] Immune-mediated nephritis appears later, usually after 14–42 weeks on immunotherapy.[13]

Tip 6. Immunotherapy is associated with "exceptional responses" in a subset of patients, and oncologists cannot reliably predict who will derive dramatic benefits

The promise of cancer immunotherapy—durable remissions often lasting years even in patients with metastatic disease—created a therapeutic revolution in oncology, with

Table 3. Screening Labs before Immunotherapy

Immune-related adverse event	*Screening labs*	*Clinical pearls*
Hepatitis	AST/ALT, bilirubin	Avoid anti-TNF agents (i.e., infliximab). Consider mycophenolate mofetil in glucocorticoid-refractory cases.
Pancreatitis	Amylase +/− lipase	Time to onset may be >10 weeks. Asymptomatic elevations in amylase/lipase are common with immune checkpoint blockade and do not require intervention.
Hypothyroidism	TSH, FT4	Time to onset may be >10 weeks. Endocrinopathies may be permanent.
Hyperthyroidism		Treat with hormone replacement and glucocorticoids. Consider
Hypophysitis	TSH, FT4, cortisol	cosyntropin stimulation test before glucocorticoid initiation
Adrenal insufficiency	Cortisol	or endocrinology consultation. Preexisting thyroid disorder
Diabetes mellitus	Fasting glucose	does not predispose patients to development of additional endocrinopathies.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

the potential for enhanced and long-term efficacy.[14] Biomarkers to predict response to treatment, which help inform shared therapeutic decision-making, are still in development. While PD-L1 immunohistochemistry represents an integral biomarker, particularly in NSCLC, it still does not reliably predict response for all patients; other biomarkers in development (e.g., tumor mutational burden, transcriptomic interferon-gamma signature) may be required to better understand the tumor immune microenvironment and predict potential therapeutic benefit.[15,16]

Given this therapeutic uncertainty, an understanding of a tumor's reasonable chance for response with an immunotherapeutic approach is crucial, especially for patients with advanced cancer in clinical decline with limited effective treatment options. Biomarkers and clinical context can provide key predictive and prognostic information. Reasonable expectations of therapy are needed, as prognosis is dynamic pending tumor response. Patients may simultaneously be hospice appropriate and a candidate for immunotherapy. If immunotherapy does not yield the desired response, the patient may benefit from direct hospice transition after cessation of therapy. Continued dialogue between palliative care clinicians and oncologists are needed to ensure continued goal-concordant care.

Tip 7. Endocrine adverse effects of immune checkpoint inhibitors can be serious, and should always be in your differential diagnosis

Immune checkpoint inhibitors can affect the normal function of several parts of the endocrine system, particularly the hypothalamic/pituitary/adrenal (HPA) axis. Two of the more serious adverse events related to this axis include primary adrenal insufficiency (adrenal crisis) and hypophysitis with secondary adrenal insufficiency. Both are critical to identify and manage early, owing to their sometimes dramatic presentation and potential long-term sequelae. The hallmarks of primary adrenal insufficiency include dehydration, hypotension, and electrolyte abnormalities (usually hyponatremia and hyperkalemia). Adrenal insufficiency is an oncologic emergency in that immediate intravenous glucocorticoids, consultation with endocrinologists, aggressive intravenous hydration, and hospitalization is warranted to avoid death. Workup of other emergent conditions in the differential requires acute care in a closely monitored environment and evaluation for similar conditions, including sepsis and cardiogenic shock.

Hypophysitis is enlargement or enhancement of the pituitary gland resulting in pan-insufficiencies of pituitary hormones. It often presents with fatigue and headache, and in more severe situations can present with vision changes (i.e., bitemporal hemianopsia). Concern for this condition increases when routine testing for thyroid function (e.g., TSH and free thyroxine [FT4]) is abnormal, or testing for fatigue with serum cortisol, adrenocorticotropic hormone (ACTH), growth hormone (GH), or prolactin is abnormal. Diagnosis of hypophysitis requires a combination of associated clinical symptoms, abnormal brain/sella imaging, and abnormal laboratory testing. Management may consist of high-dose glucocorticoids (e.g., 1 mg/kg prednisone daily), particularly if early signs of mass effect and visual disturbance are present. Early experience with checkpoint inhibitor-induced hypopituitarism reveals that most secondary hormonal deficiencies may persist for the long term, even after brain imaging abnormalities have resolved or therapy has been discontinued.

Tip 8. Immunotherapies take time to exert their maximal effects on tumors, so oncologists do not routinely perform frequent radiologic scans

Immunotherapies exert their effects on cancer cells via fundamentally different mechanisms than traditional chemotherapies. This, in part, explains why the maximal effect of these novel therapies can take months to become apparent. In some cases, there is even an initial worsening of disease, often called ''pseudoprogression.'' It may take upwards of six months to a year to achieve maximal response with immunotherapies.[17]

''Pseudoprogression,'' seen more commonly with ipilimumab, describes a relatively rare situation seen with immunotherapy use where a tumor appears larger on imaging after initiation of immune checkpoint blockade. It is hypothesized that when immunotherapies stimulate the immune response against a tumor, this results in inflammation and swelling of cells as part of the immune destruction of these malignant cells and the activation of the apoptotic process. Pseudoprogression, more common in melanoma than other tumor types, may occur in 2% to 10% or more of cases per published reports, and its occurrence may be associated with improved outcomes at one-year follow-up.[18] It is important for palliative care clinicians to recognize the difference between pseudoprogression in the first few months of immunotherapy initiation and true disease progression, which may indeed occur later after an initial improvement from immunotherapy. Caution should be practiced when discussing radiologic results with patients and ideally should include input from the treating oncologist.

Tip 9. New classes of immunotherapeutics beyond checkpoint inhibitors are coming and will have different adverse event profiles, indications, and efficacy from the current generation

Not all immunotherapeutics share the same toxicity profile, and there are nuances among the agents in this therapeutic class. While older interleukin-2-based cytokine therapy often induces short-term side effects related to hypotension, nephrotoxicity, and fever, immune checkpoint blockade often has a slower kinetic to the development of irAEs such as colitis, pneumonitis, and endocrinopathies.[19] Among immune checkpoint inhibitors, anti-CTLA-4 targeting therapy often has a more severe irAE profile compared to anti-PD-1 targeting agents.[20] Cell-based therapy such as chimeric antigen receptor T cells (''CAR-T cells'') are even newer, emerging therapies, which have a unique toxicity profile, sometimes resulting in severe cytokine release syndrome, which necessitates interleukin-6 blockade,[21] and/or neurological toxicity. These two different toxicities can occur separately, or concurrently, in a given patient, and are managed quite differently. Novel agents in clinical development targeting other immune cell types will likely induce alternative irAEs that require a multidisciplinary team to diagnose and manage. Few oncologists regret initiating a timely workup of irAEs and early intervention with immunosuppression in patients receiving immunotherapy, and a high index of suspicion with a low threshold to

initiate immunosuppression in appropriate cases represents a useful therapeutic paradigm.

Tip 10. Palliative care clinicians play an important role in addressing prognostic uncertainty experienced by oncologists and patients receiving immunotherapies

As we learn to manage new side effects, treatment schedules, and monitoring with immunotherapeutics, the role of palliative care clinicians in assisting with prognostic and diagnostic uncertainty in oncology continues to grow. Clinicians must maintain their charge of balancing hope with reality, and it is important to discuss efficacy uncertainty with our patients. While some patients may experience a dramatic response,[22] others may derive minimal benefit. With the onset of immuno-oncology, new conversations arise as follows: managing anxiety during the lengthy tumor marker discovery process, celebrating when tumor markers with targeted treatments are discovered, and grieving when they are absent.[23]

Prognostic knowledge is upended in the immunotherapy era in patients with previously predictable time courses. Patients with solid tumor stage IV malignancy once thought to be nearing end of life may now be candidates for new treatments that could even lead to cure, prolonged remissions, or clinically meaningful disease stabilization that can improve patients' overall well-being and quality of life. Oncology and palliative care clinicians should engage in continued education and dialogue to assist patients and caregivers with advance care planning in the setting of prognostic uncertainty. While tumor-directed therapy at the end of life has previously been recognized to compromise quality of life,[24,25] immunotherapeutics challenge this assumption.

Conclusions

As palliative care involvement in the care of patients with cancer continues to grow and move further upstream, palliative care clinicians will increasingly be faced with the challenges presented by evolving cancer-targeted treatments such as immunotherapies. The associated unique adverse events compared to conventional cytotoxic chemotherapies pose their own diagnostic and treatment dilemmas, and supportive care practices continue to evolve among these agents. In addition, palliative care specialists are challenged with managing patient expectations and uncertainty regarding outcomes, made more difficult with the presence of ''exceptional responders.'' The role of palliative care specialists in the care of cancer patients receiving immunotherapies will continue to grow with multiple opportunities to collaborate with our oncology colleagues to provide the best care now.

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