Original Article

Immune-Related Adverse Events in the Older Adult with Cancer Receiving Immune Checkpoint Inhibitor Therapy

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ABSTRACT

Objective: Older adults with cancer (OAC) may be at elevated risk for immune-related adverse events (irAEs) during immune checkpoint inhibitor (ICI) therapy due to the normal organ function changes of aging, as well as related to a higher prevalence of comorbid conditions compared to younger patients. The importance of high-quality nursing care cannot be overstated for this population, including proactive symptom assessment, management, and coordination of care. The purpose of this paper is to describe the unique challenges faced by OAC receiving ICI drugs. **Methods:** We present both a case study and the results of a single-institution retrospective study from a large, urban US National Cancer Institute– designated comprehensive cancer center. The retrospective study examined the frequency and intensity of irAEs experienced by patients aged 75 years or older who received ICI therapy between January 2016 and December 2018 for melanoma. **Results:** We reviewed the records of 38 OAC (age range 75–92 years) with locally advanced or metastatic melanoma who received pembrolizumab, nivolumab and/or ipilimumab. Median length of therapy was 7.4 months, and median time to onset of irAEs was 81 days. Approximately half (47%) of the patients experienced Grade 1–3 irAEs, and discontinued therapy related to inability to tolerate the ICI more frequently than was reported in clinical trials (24%). **Conclusions:** OAC who receive ICI therapy frequently experience irAEs that may result in treatment interruption, discontinuation or long-lasting toxicity. Nurses are well positioned to provide support to this vulnerable population.

Key words: Aging, ipilimumab, melanoma, nivolumab, pembrolizumab, symptom assessment

Introduction

Although the origin of immunotherapy may date back to Coley's toxins in 1893,[1] meaningful understanding and therapeutic use of agents such as interferon and interleukins to influence innate immune processes did not advance until the 1980s.[2] Most recently, oncology practice has been revolutionized by the development of monoclonal antibodies targeted to specific molecules that are overexpressed in the tumor microenvironment, such as the programmed cell death protein and its ligand (PD-1 and PD-L1) and the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). Blockade of these molecules prevent tumor cells from escaping immune detection and reactivate cytotoxic T cells to recognize and destroy these

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cancer cells.[3] This class of drugs is often referred to as immune checkpoint inhibitors (ICIs), so named for the innate regulatory functions of these molecules that keep immune responses appropriately in check under normal circumstances.

However, manipulation of the immune system is not without risk; use of these agents may result in autoimmune effects in multiple organ systems not typically encountered during cancer treatment. Adverse events (AEs) are classified according the National Cancer Institute's Common Terminology Criteria for AEs[4] (CTCAE). The CTCAE standardized criteria organizes toxicities by organ system with a general scale of 0 (no toxicity) to 5 (death). Grade 1 and 2 are categorized as mild and moderate AEs in most cases with minimal to no interruption to a patient's plan of care. Grade 3–4 toxicities are considered more severe and require medical intervention, potential hospitalization, and limitation of further treatment. With the emergence of unique AEs specific to the ICIs, several groups have published guidance for the identification and management of immune-related AEs (irAEs).[5-8]

The clinical evidence supporting the efficacy of ICIs to treat diseases such as melanoma, lung, renal, and other cancers is strong and growing.[9-15] Although we consider them as a single drug class, evidence indicates that there are differences in the mechanism of action and most frequently presenting irAEs between the anti-CLTA-4 and anti-PD-1/PD-L1 agents.[16] The exact immune dysregulations associated with the development of irAEs are not fully understood, but the similarity to known autoimmune disorders is logical considering that the normal functions of immune checkpoint proteins are to maintain homeostasis and de-escalate the systemic immune response after a pathogen has been cleared.[17] The most common organ systems to experience irAEs included the endocrine, gastrointestinal, pulmonary, skin, and musculoskeletal systems, and there appear to be some drug-specific effects. Ipilimumab is frequently associated with hypophysitis and colitis, possibly due to an increase in CTLA-4 binding sites in the pituitary gland and gastrointestinal tract.[18,19] Changes in thyroid function and pneumonitis are more commonly seen with anti-PD-1/L1 therapy and may relate to interactions with a rise in antithyroid antibodies or that this artificial manipulation of PD-1 dysregulates immune self-tolerance, leading the patient's body to attack itself.[16,20] Unlike traditional chemotherapies where AEs may appear at predictable intervals within each treatment cycle, irAEs may present at any time, including months after treatment initiation and can be life-threatening without early recognition and management.[21-23]

Older adults with cancer and immune checkpoint inhibitor therapy

Normal aging results in alterations to organ systems such as thinner skin, decreased renal, hepatic, and marrow function.[24] Older adults more frequently accumulate comorbid conditions such as diabetes, osteoarthritis, cardiovascular, and other clinical problems that may increase their risks of AEs during cancer treatment.[25] Although ICIs are frequently offered to older adults with cancer (OAC) due to the perception that they are less toxic than traditional chemotherapy[26] there are few data to support this view.[27]

Even though globally approximately 50% of cancer incidence occurs in people age 65 years or older,[28] OAC are proportionally underrepresented in clinical trial participation,[29,30] providing few data to guide practice for this population. Fortunately, several reviews examining available response and survival outcomes have concluded that older adults appear to derive similar anticancer benefit from ICIs as do their younger counterparts.[27,31,32] However, little is known about whether the incidence or severity of irAEs among older adults receiving ICI therapy differs from other age groups. Several retrospective reviews focused on this issue have not found statistically significant differences in irAEs based on age.[31,33,34] However, since most older adults receive ICIs outside of a clinical trial, "real world" data from registry or electronic health record (EHR) datasets may be necessary to truly understand outcomes for this population.[26]

Nursing care

Excellent nursing care, including initial and ongoing patient and caregiver education, proactive symptom assessment, active management, and coordination of care through the documentation of baseline and incidental irAEs is key to the successful support of older adults receiving ICI therapy.[35] Nurses must continuously build knowledge about the mechanisms of action and emerging toxicities and evidence-based management strategies for these new drugs. The purpose of this paper is to describe the unique challenges faced by OAC receiving ICIs, highlighted through a case study and single-institution retrospective study results so that nurses can most effectively support this potentially vulnerable population.

Immune checkpoint inhibitor therapy nursing management

The management of irAEs begins at the first mention of the proposed treatment for all patients, especially with OAC. Health-care providers are tasked with performing a thorough baseline examination, extensive laboratory assay,

review of medical history and concomitant medications, and evaluation of the patient's support system.

For nurses, this initial meeting with the OAC may take longer than other routine visits. The OAC may experience cognitive, visual and hearing challenges that could impact the visit. The CDC offers strategies such as speaking slowly and repeating, reducing the amount of text in handouts and increasing font size, and using plain language to communicate directions and advice that need to be followed.[36] Nurses should take care to make sure that OACs have a support system who can assist with care, transportation, and medical management as health literacy and polypharmacy are frequent issues for the older adult. If the patient presents for care alone, it is pertinent to confirm with whom health information can be discussed and that the correct institutional documentation is in the chart. Nurses should also assess the patient's comfort level with various means of communication and best ways to contact the patient.

During the initial meeting nurses can assess and document baseline symptoms related to the current disease status as well as past medical diagnoses utilizing the CTCAE grading scale prior to the patient's receipt of treatment. This will aid in the future differentiation between an exacerbation of a baseline condition or presentation of new possible irAE. As part of medication teaching for ICIs, nurses should stress that any new symptom should be reported to the healthcare team as irAEs can present in multiple organ systems and at any time during or after treatment.[3,8]

While patients are receiving therapy, it is essential to maintain communication. Points of contact between drug administrations can help nurses monitor and circumvent potential side effects. Older adult patients may be hesitant to report side effects to their health-care providers for fear that their treatment may be withheld. Maintaining communication helps to build trust and reinforces the teaching that patients should communicate any new side effects. It also gives nurses a chance to ensure that the OAC has not seen any other providers or been prescribed additional medications that could possibly interact with their treatment.

Although an irAE may manifest in any organ system, when working with OACs nurses should practice extra vigilance in systems that are already affected by the process of aging. Monitoring for changes in activities of daily living (ADL), endurance or stamina may be indicative of musculoskeletal or respiratory changes such as arthralgias or pneumonitis. A deviation from baseline performance of ADL could be suggestive of underlying irAEs such new or increased joint pain. Weight loss may indicate anorexia or cognitive changes.

It is vital for the nurse to function as a member of the health care team and to have a working knowledge of potential irAEs with ICIs. Seemingly insignificant patient reports and minor fluctuations in laboratory values, such as endocrine values, may lead to the discovery of early onset irAEs.[23] When new symptoms arise, the nurse must work with the healthcare team to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before labeling the symptom an irAE. Once determined to be an irAE, the symptom can be managed per general and specific guidelines.[5-8]

Briefly, treatment generally continues during Grade 1 toxicities with close monitoring except for some neurologic, hematologic, and cardiac toxicities. For Grade 2 toxicities, treatment may continue or be held until symptoms or laboratory values return to Grade 1 or less. A weight based steroid taper may be implemented as well. Grade 3 toxicities are treated like Grade 2 toxicities with the addition of mandated drug holds and referrals to system-specific specialists. In the setting of a Grade 3 rash, it would be advised to hold the therapy, administer a weight-based steroid taper, and refer to a dermatologist.[5-8] Table 1 shows the major grading and management points, using rash as an exemplar. When utilizing steroid tapers, make sure to provide the OAC with clear instructions of dosing, frequency, and supportive medications. A calendar with the appropriate doses and dates is very helpful.

In the care of the OAC, unforeseen toxicities may arise as well. The financial impact as well as the potential morbidity from the irAEs experienced by OAC receiving ICIs is unclear. Estimated annual costs of checkpoint inhibitor agents may reach $150,000 for single agents or over $250,000 for the combination of ipilimumab and nivolumab,[37] resulting in daunting coinsurance amounts for patients with Medicare part A/B with no secondary insurance.[38] Indirect costs such as the act of traveling to the institution and the costs of over the counter or prescription medications for their care may also result in financial hardship for patients. Much like nurses advocate for referrals to dermatologists and endocrinologists they should also advocate for financial counselors, social workers, case managers, and/or patient navigators within the institution.[39]

To illustrate these points, we present the case study of a patient treated at our institution who faced significant physical and financial challenges during treatment.

Case study

DG, aged 78 at first presentation (*fictionalized identifiers*), is known to a major academic center for the management of her localized myxofibrosarcoma. Prior to pursuing treatment on a clinical trial, the center had coordinated treatment in

Table 1: Example of immune-related adverse events grading and management of rash[5-8]

Severity of skin toxicity	Examples of management	Follow-up
Grade 1: Not affecting quality of life; able to control with topical or oral regimen, <10% BSA	Topical emollients with ingredients such as petrolatum, lanolin, mineral oil, and dimethicone Oral or topical antihistamine Topical steroid (i.e., triamcinolone acetonide 0.5%)	ICI dose/schedule not affected Confirm response to topical interventions
Grade 2: May have psychosocial impact, limiting ADL, 10%-30% BSA, may or may not be associated with pruritus or tenderness	Antihistamine Topical steroid Dermatology consult	Consider biopsy Consider delay in ICI therapy Possible oral steroid taper if poor response to topical steroids Monitor for response
Grades 3-4: Grade 2 symptoms, associated with possible local super infection and oral antibiotics indicated, >30% BSA	Antihistamine Oral or IV steroid Dermatology consult	Biopsy Treatment delay or discontinuation 1.0-2.0 mg/kg steroid dosing over month long taper Hospitalization

BSA: Body surface area; ADL: Activities of daily living; IV: Intravenous; ICI: Immune checkpoint inhibitor

the community with single-agent pembrolizumab. The patient experienced Grade 2 irAEs of hypothyroidism and hypophysitis, both requiring replacement doses of Synthroid and hydrocortisone before returning to the academic center to pursue the clinical trial with combination therapy including pembrolizumab. The Medical Oncologist clearly explained and documented potential AEs and the RN established family contacts, documented baseline toxicities, reviewed medications and contacted medical social work to discuss transportation in the setting of frequent visits. The patient was unable to utilize public transit due to gait changes and mobility challenges. Before trial therapy began the patient reported baseline G 1 pruritus, dry skin, maculopapular rash (to chest), and fatigue. DG remained on treatment for 3 months and experienced a dramatic decrease in her disease burden. Unfortunately, the expense of traveling back and forth to the center became a significant burden and the patient did not qualify for any additional financial assistance. The RN coordinated transition back to the community provider to restart single-agent pembrolizumab. Several months later, the patient contacted the academic center asking to speak with the RN. In conversation she stated, "you always told me to call you if something was wrong, and something is very wrong." The patient reported a Grade 3 blistering rash with Grade 2 pruritus that the patient chose to manage with calamine lotion and Preparation H. Treatment to that time included holding further dosing with pembrolizumab but concerns about interactions with patient's adrenal replacement dosing of hydrocortisone stalled further interventions. The RN contacted the treating team at the academic center and telehealth conversations were initiated with the help of the patient's family members. Topical and oral steroids were prescribed, appropriate over the counter anti-itch lotions recommended, and a referral to dermatology was made. The patient required a month and a half long steroid taper and eventually was treated with Omalizumab (Xolair) per Dermatology.

This case illustrates the importance of coordination of care, proactive education, and nurse-patient communication. Challenges in this patient's care included the different sites of the treatment administration over many months of care and the late exacerbation of the patient's previously mild rash and pruritus. In addition, the patient's inability to remain on a clinical trial that was positively affecting her cancer due to financial constraints and limited transportation options is notable. Because of the relationship that had been forged between the RN and this patient, she was able to appropriately advocate for the management of her symptoms and alleviate the negative impact that they were having on her life.

Single-institution retrospective review of immune-related adverse event in older adults with cancer

To examine the impact of ICI therapy, older adults at our institution on a larger scale, we conducted a retrospective review to assess the type and frequency of irAEs experienced by this vulnerable population.

Methods

After institutional review board approval was obtained, EHR data from a single, urban NCI-designated comprehensive cancer center reviewed all available cases treated between January 1, 2016, and December 31, 2018 to identify a cohort of patients aged 75 years or older who received the ICI drugs nivolumab, pembrolizumab, and/or ipilimumab to treat locally advanced or metastatic melanoma. Patients were excluded if they received ICIs on clinical trials or were actively being treated for a secondary malignancy. Fifty-five cases were found, and 38 cases met inclusion criteria and were reviewed [Figure 1]. Seven patients were ineligible due to clinical trial participation and 10 received ICIs for a second malignancy.

Data collection and analysis

Ambulatory clinic, inpatient, and infusion center notes were reviewed to identify irAEs by two investigators

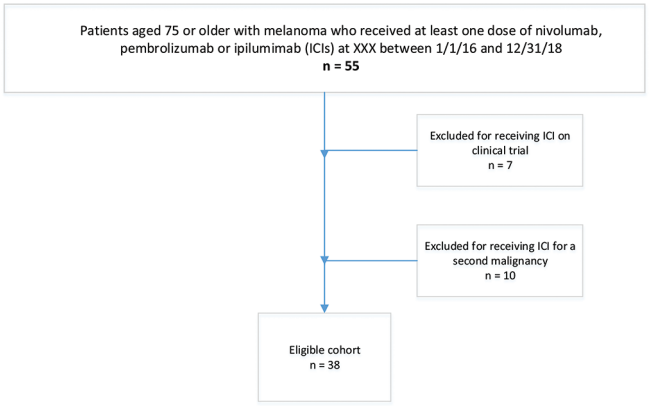

Figure 1: STROBE diagram

(MKK and KLF) independently, using a standardized abstraction template. The Eastern Cooperative Oncology Group (ECOG) score closest to the start of the first recorded ICI and ending date of the last administration of any ICI were abstracted. Where a CTCAE grade was documented by a clinician, the toxicity category, grade, date, and source document type (e.g., medical oncology visit note and specialist consultation note) were directly abstracted as recorded in the EHR. Mentions of actual or likely irAEs found but not graded (e.g., "the patient reports mild rash") were assigned a tentative CTCAE grade by the investigator, recording the source document, date, and text supporting the grade. Results for each patient case were then reviewed by the research team and adjudicated until consensus was achieved.

Results

A total of 38 patients were evaluated for this retrospective chart review. Patients'ages ranged from 75 to 92 years. The cohort was predominantly male ($n = 27$, 71%) and all were Caucasian. Most patients were diagnosed with Stage IV metastatic melanoma ($n = 34$, 89%) and 11% ($n = 4$) with Stage IIIb or IIIc disease. One patient was known to have a preexisting autoimmune condition prior to beginning ICI therapy. Comparison of baseline pretreatment ECOG scores (mean = 0.76, range 0–3) to posttreatment ECOG scores (mean = 1.5, range 0–5) demonstrated significant decrease in performance status for the overall cohort ($t = -3.62$; df 74 $P = 0.000,536$). The mean length of treatment for patients in this retrospective review was 226.4 days or 7.4 months. Patients discontinued therapy for one of four reasons: progression of disease, intolerant of ICIs as evidenced by significant irAEs, complete response to therapy, or death. Approximately 42% ($n = 16$) of patients discontinued therapy related to progression of disease and lack of response to ICI therapy. An estimated 24% ($n = 9$) of patients discontinued therapy related to an irAE, a higher rate than that reported by the manufacturer's ICI prescribing information.[40-42] Eight percent ($n = 3$) of patients experienced a complete response to therapy and discontinued therapy as a result.

Tolerability

About half of the patients ($n = 18$, 47%) had one or more gradable toxicity, ranging from Grade 1–3. The median onset of irAEs regardless of grade was 81 days. A total of 7 (18%) of patients experienced Grade 1 toxicity, including the dermatologic, hepatic, pulmonary, and endocrine systems. An estimated 29% of patients ($n = 11$) in this retrospective review experienced a Grade 2 irAE including hypothyroidism, primary adrenal insufficiency, myasthenia gravis, polymyalgia, rash, transaminitis, and colitis.

Grade 3 toxicities were found in nine of 38 patients (23.7%), including hypophysitis, pneumonitis, myocarditis, and myasthenia gravis. Four patients experienced severe symptoms of colitis, three while receiving combination therapy of ipilimumab plus nivolumab, experiencing >7 bowel movements above baseline associated with abdominal pain. These patients required inpatient hospitalization for fluid resuscitation, immunosuppression in the form of IV corticosteroids in the acute phase and second-line immunosuppression in the form of infliximab (5 mg/kg) to address colonic inflammation.

Discussion

Although older adults may frequently receive ICI therapy, less is known about the population specific effects of these regimens. Prompt recognition of these unique toxicity profiles by nurses could allow for patients to avoid a severe toxicity, inpatient hospitalization, and discontinuation of ICI therapy. Ongoing nursing education is imperative to understand the mechanism of action of these drugs, toxicity profile, and triage of management. Further research is needed to compare the experience of the older adults receiving these agents with those that are 65 years or younger, such as through the development of a multicenter registry that could support nursing inquiry within a larger sample with more heterogeneity in gender and race. In addition, multicenter efforts may enhance our understanding and practice improvements such as best practices for consistency of irAE assessment, documentation and management strategies, optimal timing for nursing contacts with patients between clinic visits, and most effective modes of patient education.

Conclusions

Older adults who receive ICI therapy may be at elevated risk for adverse events due not only to the expected toxicities

of these drugs, but also related to the normal physiologic changes associated with aging. This review illustrates that ICI therapy may result in treatment interruption, discontinuation or long-lasting toxicity among OAC. By establishing strong lines of communication and proactive education at the start of treatment, nurses are better able to support older adult patients during their therapy.

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Conflicts of interest

There are no conflicts of interest.

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