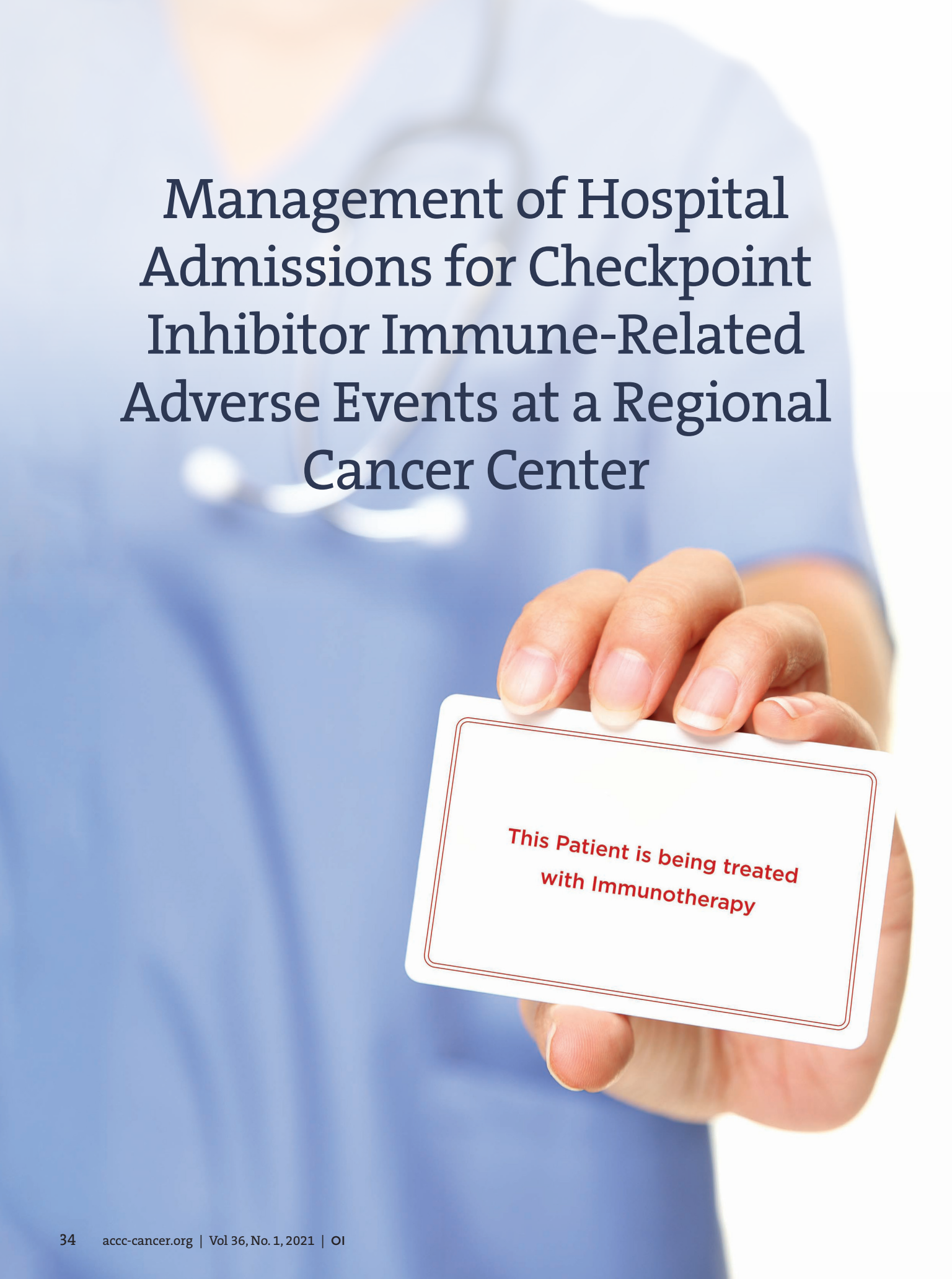
Management of Hospital Admissions for Checkpoint Inhibitor Immune-Related Adverse Events at a Regional Cancer Center



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In Brief

The use of immune checkpoint inhibitors in oncology has surged over the past decade and is projected to continue increasing for years to come. With the forecasted rise of immunotherapy use, it is now more important than ever to ensure the safety of patients who are receiving these agents. The toxicity profiles of immunotherapy agents are vastly different from traditional cytotoxic chemotherapies. Immune-related adverse events (irAEs) can lead to life-threatening outcomes if not treated appropriately. Incidence of severe irAEs (grade 3 or 4, which may require hospitalization) varies across publications, and minimal data are available to indicate what percentage of hospital admissions of immunotherapy-treated patients are due to irAEs. Determining this figure may clarify the actual hospitalization burden of irAEs on hospital systems. In addition, evaluating health systems' clinical management of irAEs can uncover areas of improvement in quality of care for immunotherapy treated patients. In June 2018, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) released guidelines on the management of irAEs. St. Luke's Health System used these guidelines to evaluate where the health system consistently met these benchmarks and identify areas of improvement.

The global cancer immunotherapy market is expected to grow from $61.9 billion in 2016 to $119.39 billion by 2021.[1] Much of this growth is due to immunotherapy's ability to create durable anti-tumor responses and the wide versatility of indications ranging from various solid tumors to hematologic cancers, with new indications continuing to be approved.[2,3] Immunotherapy can over-activate T-cell function and result in immune-related adverse events. These irAEs most commonly occur in the following organ systems with respective presentations:

- Skin (dermatitis)
- Gastrointestinal tract (colitis)
- Lungs (pneumonitis)
- Liver (hepatitis)
- Endocrine system (thyroiditis or hypophysitis).

Early detection and treatment with corticosteroids are essential to limiting the severity and duration of these irAEs.[4] If untreated, high-grade irAEs can lead to severe complications and sometimes fatal outcomes.

Massachusetts General Hospital reported that the number of inpatient admissions tied to severe irAEs rose threefold over five years.[5] With the widespread use of immunotherapy over the last decade, institutions may not be inclined to recognize irAEs. Moreover, emergency medicine and internal medicine practitioners may be the first providers to encounter patients experiencing an irAE and may not be aware that irAEs differ vastly in their toxicity profile compared to traditional cytotoxic chemotherapies. Not only do these adverse events also manifest much later (months after treatment initiation) compared to traditional cytotoxic agents, the specific organ systems in which these adverse events take place differ as well.[6]

Another complicating factor is that irAE incidence rates leading to an emergency department (ED) or inpatient admission have yet to be identified. Incidences of all grades of irAEs widely range from 15 to 90 percent across different studies; the rate of severe irAEs requiring corticosteroids and withdrawal of immunotherapy ranges from 0.5 to 13 percent.[7] Though minimal data exist to indicate what proportion of all immunotherapy-treated patients are admitted to the hospital due to irAEs, determining this percentage would help clarify the hospitalization burden that irAEs put on a health system.

In addition, evaluating a health system's clinical management of these adverse events will identify opportunities to improve the treatment of these patients. At St. Luke's Health System, we have a multitude of ED and hospital sites that vary geographically from urban to rural areas. These facilities are frequently on the front line of examining patients experiencing a severe irAE. Gauging our performance across sites will also allow St. Luke's Health System to discover areas for improvement in the system, as well as for each individual site. Our team at St. Luke's Health System used NCCN and ASCO guidelines on the management of irAEs to identify the standard of care and then evaluate benchmarks met and areas for improvement.[7,8]

Our Study

Our initial goal was to ascertain the overall rate of ED visits and inpatient hospitalizations due to irAEs. A second goal was created to establish a tool to evaluate the health system's performance in the clinical management of irAEs. The results of this evaluation are intended to identify areas of improvement and then create educational initiatives to address these areas throughout the entire health system.

The first step was to conduct a clinical review of all immunotherapy-treated patients who were admitted to a St. Luke's Health System ED or inpatient facility from March 2017 to March 2018. Specifically, we did a retrospective chart review on patients who received a dose of immunotherapy between March 2016 and March 2018 with any of the following agents:

- Ipilimumab
- Atezolizumab
- Nivolumab
- Avelumab
- Pembrolizumab
- Durvalumab.

Patients who experienced an irAE-related ED or inpatient admission between March 2017 and March 2018 were then included as part of the analysis. IrAEs have been documented to occur even a year after the last dose of immunotherapy.[9] Therefore, extending this two-year time window allows adequate capture of all patients who experienced an irAE over a one-year period. Next, we evaluated interventions made during the treatment phase and after the diagnosis was confirmed. Metrics for evaluation included the presence of a medical oncology consult and appropriate medication management administered in the correct dose and timing.

ED and inpatient admissions were determined to be associated with an irAE if the diagnosing physician explicitly stated diagnosis of an irAE in electronic health record documentation. However, if in a future encounter the patient's symptoms are diagnosed as an irAE but in the initial encounter they were not, both encounters are still associated with an irAE diagnosis. For example, a patient on immunotherapy is admitted to the ED for severe diarrhea and the physician incorrectly associates the diarrhea with food poisoning; the patient is discharged after parenteral hydration. Later, the patient is re-admitted to the ED with worsening diarrhea. Medical oncology is consulted this time, and the consulting oncologist diagnoses the patient with irAE-related colitis. Both the initial and subsequent ED encounters are considered irAE-related.

The following baseline information was recorded from patients who experienced an irAE:

1. Date of admission
2. Length of stay (if an inpatient admission)
3. Immunotherapy agent(s) used
4. Malignancy
5. irAE type and grade
6. Admission location region (rural or urban).

Grading an irAE was estimated by comparing the symptoms recorded in the electronic health record documentation and/or lab values at the time of the encounter, along with the grading system of irAEs outlined in NCCN and ASCO guidelines.[7,8] Each irAE admission was then evaluated with the following evaluation criteria that were constructed from ASCO and NCCN guidelines:[7,8]

1. Was there a medical oncology consultation?
2. Were corticosteroids given at the appropriate dose (within 10 percent of the recommended dose)?
3. Post-discharge, were corticosteroids properly tapered over a greater than four-week period?
4. If the patient was evident to have steroid-refractory disease, was a secondary agent administered at the appropriate time frame?
5. If additional adjunct medications were appropriate in the management of the irAE, was it administered at the appropriate dose and timing?

In cases where patients are not demonstrating adequate responses to corticosteroids alone after 48 to 72 hours, a secondary immu-

Table 1. Secondary Agents

irAE	Clinical Scenario	Secondary Agent
Colitis	G2-G3: If symptoms persist for three to five days or recur after improvement with steroids	Infliximab
	Refractory to infliximab or contraindication to TNF-alpha blocker	Vedolizumab
Hepatitis	G3-G4: Corticosteroid refractory or no improvement after three days	Mycophenolate Mofetil
	G3: Corticosteroid refractory or no improvement after three days	Azathioprine
Pneumonitis	G3-G4: No improvement after corticosteroid use for 48 hours	Infliximab Mycophenolate Mofetil IVIG Cyclophosphamide

Notes: G2 = Grade 2; G3 = Grade 3; G4 = Grade 4; IVIG = Intravenous immunoglobulin.

Table 2. Adjunct Agents

irAE and Grade	Adjunct Agent
Colitis (G2-G3)	Topical emollients Oral histamines Topical corticosteroids
Colitis (G2)	Loperamide for consideration
Pneumonitis (G2-G4)	Empirical antibiotics for consideration in G2 Definite empirical antibiotics in G3-G4

Notes: G2 = Grade 2; G3 = Grade 3; G4 = Grade 4

Immunotherapy is an oncology-based drug class, which has become relevant to other disciplines, such as internal medicine, critical care, and emergency medicine.

nosuppressive agent may be used to assist in controlling irAE symptoms. Unlike corticosteroids, which are universal to most irAEs, secondary agents are distinct in their use with particular irAEs. Table 1, page 37, identifies the different secondary agents that can be used for various irAEs. In certain grades of severity, the irAE guidelines recommend non-immunosuppressive supportive care agents or antibiotics that may aid in the care of the irAE, alongside immunosuppressive agents. Table 2, page 37, identifies the adjunct agents that can be used for different irAEs.

Our Results

Using a computer algorithm to detect patients who met the established criteria, 295 patients were identified. After retrospective chart review of all 295 patients, 13 unique patients underwent 16 ED or inpatient admissions due to irAEs, which resulted in a hospitalization rate of 4.4 percent (Table 3, page 38).

Of the 16 total encounters, an irAE diagnosis was missed in 6 ED admissions. In all 6 cases, there was no medical oncology consult and 5 out of the 6 cases were located at rural sites. These encounters were determined to be an irAE in one of two ways: (1) the patient was re-admitted to the cancer center for recurrent symptoms and (2) during a clinic visit, an oncologist attributed the symptoms to an irAE, despite the ED provider assigning the symptoms to another cause.

Of the 16 cases, 10 of which were correctly diagnosed, there were 40 possible actions where an irAE could have been managed appropriately. Not every category listed in Table 3 is applicable for every case. For example, a patient managed adequately on corticosteroids alone would not need a secondary agent; therefore, that category would not apply to that patient. In the mis-diagnosed cases, the only applicable action was a medical oncology consult.

Out of 40 possible actions, 24 (60 percent) were fulfilled. The remaining 16 opportunities for improvement are shown in Table 4, page 39.

The two most significant areas of improvement with the most instances are no medical oncology consult done and the under-dosing of steroids (greater than 10 percent discrepancy), with other areas having less frequency (Table 5, page 39).

(continued on page 39)

Table 3. Evaluation of irAE Encounters

Encounter	Patient	Agent(s)	Malignancy	irAE and Grade	Area	Admission	Consult	Dosing	Schedule	Secondary Agent	Adjunct Agent
1*	1	Nivolumab	Pancreatic adenocarcinoma	G2 Myositis	Urban	ED	✗				
2*	2	Nivolumab/ Ipilimumab	Melanoma	G3-G4 Guillain-Barre syndrome	Rural	ED	✗				
3*	3	Pembrolizumab	NSCLC	G2 Colitis	Rural	ED	✗				
4*	4	Nivolumab	Melanoma	G2 Colitis	Rural	ED	✗				
5*	5	Nivolumab	Cholangiocarcinoma	G2 Colitis	Rural	ED	✗				
6*	6	Nivolumab/ Ipilimumab	Melanoma	G2 Colitis	Rural	ED	✗				
7	7	Ipilimumab	Melanoma	G3 Colitis	Rural	Inpatient	✓	✗	✓	✗	
8	8	Durvalumab	NSCLC	G2 Pneumonitis	Urban	ED	✗	✗	✗		
9	9	Durvalumab	NSCLC	G4 Pneumonitis	Rural	Inpatient	✓	✓		✗	✓
10	10	Nivolumab	NSCLC	G3 Colitis and G3 pneumonitis	Urban	Inpatient	✓	✓	✓		✓
11	11	Nivolumab	Melanoma	G4 Colitis	Urban	Inpatient	✓	✗		✓	
12	12	Nivolumab/ Ipilimumab	Melanoma	G3 Colitis	Urban	ED	✓	✓	✓		
13	13	Ipilimumab	Melanoma	G2 Peripheral neuropathy	Rural	Inpatient	✓	✓	✓		✓
14	2	Nivolumab/ Ipilimumab	Melanoma	G3-G4 Guillain-Barre syndrome	Rural	ED	✓	✗	✓		✗
15	4	Nivolumab	Melanoma	G3 Colitis and G2 hepatitis	Rural	Inpatient	✓	✓	✓		
16	5	Nivolumab	Cholangiocarcinoma	G3 Nephritis and G1 colitis	Rural	Inpatient	✓	✗			

Notes: G2 = Grade 2; G3 = Grade 3; G4 = Grade 4; NSCLC = non-small cell lung carcinoma.

* In this encounter, the diagnosis of an irAE was incorrectly missed, but it is still affiliated with an irAE due to a subsequent encounter eventually obtaining the accurate diagnosis.

✓ In this encounter, the irAE event was eligible for this category of intervention and the action was fulfilled.

✗ In this encounter, the irAE event was eligible for this category of intervention and the action was **not** fulfilled.

☐ In this encounter, the irAE event was **not** eligible for this category of intervention.

In light of this analysis, we revised St. Luke's Health System's immunotherapy patient handout to add a section on irAEs, including details on possible symptoms and when to contact the clinic for further workup.

Table 4. Areas of Improvement

Area of Improvement	Number of Occurrences
No medical oncology consult	7
Under-dosing of corticosteroids	5
Secondary medication not given at appropriate time	2
Neglect to taper steroids	1
Wrong timing of adjunct medication	1
Total	**16**

(continued from page 37)

Exploratory Outcomes

Two additional outcomes were evaluated: (1) 30-day mortality post-admission and (2) median length of stay (for inpatient admissions).

Out of the 13 unique patients who experienced institutional encounters for severe irAEs, 5 died within 30 days of admission. Two of these patients died due to disease progression, and the remaining three patients' cause of death was a severe irAE. Two of the irAE-related deaths were gastrointestinal related (severe bowel obstruction and bowel necrosis), and the third irAE-related death was due to severe pulmonary pneumonitis progressing into fibrosis and respiratory failure. Therefore, the irAE-related mortality rate at St. Luke's Health System is 1 percent. All three patients with irAE-related deaths were under-dosed corticosteroids, ranging from 20 to 38 percent. Two of these patients were eligible to use a secondary agent, but none was used. Although there was potential for improvement in the management of these patients, it is difficult to predict whether adequate corticosteroid use and a secondary agent could have prevented these deaths, due to the severity of their irAE conditions.

The median length of stay for inpatient admissions was four days.

Lessons Learned

Immunotherapy is an oncology-based drug class, which has become relevant to other disciplines, such as internal medicine, critical care, and emergency medicine. At St. Luke's Health System, we have a low irAE-related ED and inpatient admission rate of 4.4 percent. This could be due to several factors; for example, the reporting incidence of severe irAEs has been low, showing that our incidence is consistent in the range reported in previous

Table 5. Incidence of Under-Dosing

Encounter	Patient	Diagnosis	Admission	Expected	Administered	% Discrepancy
7	**7**	G3 Colitis	Inpatient	100 mg	80 mg	20%
9	**9**	G2 Pneumonitis	ED	80 mg	50 mg	38%
11	**11**	G4 Colitis	Inpatient	100 mg	75 mg	25%
14	**2**	G3-4 Guillain-Barre syndrome	Inpatient	200 mg	120 mg	40%
16	**5**	G3 Nephritis and G1 colitis	Inpatient	100 mg	60 mg	40%

Dosing was based on prednisone or prednisone equivalents.

literature.[7] Another possibility is that a proportion of irAEs at our institutions are being adequately managed in the outpatient setting, therefore preventing the need for ED or inpatient care.

However, our study revealed several areas or improvement that we can address when patients are admitted to the ED or inpatient setting for irAEs. Firstly, there have been incidents where the emergency medicine provider does not consider an irAE as part of the diagnostic differential when seeing an patient with an irAE. In all of these incidents, there was no medical oncology consult. Therefore, education on irAEs should be provided to emergency department physicians and patients to increase awareness and improve accuracy in correct irAE diagnosis. In light of this analysis, we revised St. Luke's Health System's immunotherapy patient handout to add a section on irAEs, including details on possible symptoms and when to contact the clinic for further workup. In addition, we provided a brief education session during our System Emergency Medicine Meeting to spread teaching materials across multiple practicing groups, which include rural emergency medicine providers. At this meeting providers were also encouraged to consult our on-call medical oncologist whenever a patient has a history of immunotherapy treatment and presents unfamiliar symptoms. A consult in all of these cases may likely have improved accuracy in diagnoses.

For numerous reasons, irAEs can be especially difficult to diagnose. Symptoms of irAEs can be confounded with various other differential diagnoses. For example, non-specific symptoms such as nausea, malaise, and diarrhea resulting from colitis may easily be assigned to another cause in a medically complex patient. Although irAEs commonly occur at certain organ systems, it is possible that they can reach any organ system, making the challenge of accurately diagnosing these events even more difficult. This is evidenced by several of our patients experiencing the rarer irAEs (Guillain-Barre syndrome, nephritis, etc.). Lastly, irAEs can occur even up to a year after discontinuation of therapy.[9] Therefore, the risk of an irAE continues to exist when patients have not been receiving therapy for an extended period of time. Because the physician doing the initial patient evaluation may not even consider immunotherapy as a cause, it is crucial for the medical oncologist to participate in the continued care of a patient with a history of immunotherapy.

Accurate diagnosis could prevent re-admissions. After one patient was misdiagnosed on their first ED admission (encounter 2), the patient was re-admitted to the ED (encounter 14). Other patients were also misdiagnosed after their initial ED visits (encounters 4 and 5) and were later re-admitted to the inpatient setting (encounters 15 and 16). Therefore, correct diagnosis on the first encounter would avert subsequent encounters.

The second area to address is the adequate dosing of corticosteroids. One possible barrier to proper dosing is that this large prednisone dosage (1 mg/kg/day) is atypical and does not match other methods of dosing. Other indications for corticosteroids (e.g., chronic obstructive pulmonary disease) have set doses of lower strengths, so these errors could have resulted from incorrect extrapolation from other indications. The second source of errors is the particularly high doses of corticosteroids. For example, for Guillain-Barre syndrome, the recommended dosage starts at 2 mg/kg/day of methylprednisolone,[6] which is 2.5 mg/kg/day of prednisone and considerably higher than the typical 1 mg/kg/day. Proper education and diligent referral to the NCCN/ASCO guidelines will eliminate these errors.

Several members of the healthcare team can ensure that this proper dosing is done, including pharmacists, internal medicine physicians or emergency medicine physicians seeing patients, and consulting oncologists. To improve patient care at our institution, we distributed our study results, as well as instruction on the management of irAEs. Adequate corticosteroid dosing and proper use of secondary agents were the emphasized areas of improvement. This information was distributed via the internal medicine newsletter for internal medicine physicians, via the Pharmacy Grand Rounds Conferences for inpatient pharmacists, and to the cancer institute's medical director for medical oncologists.

Education on irAEs is necessary to increase awareness and improve accuracy in the diagnosis of irAEs for emergency department physicians. Education to inpatient oncology practitioners will help to ensure proper corticosteroid dosing and use of secondary agents in the management of irAEs.

Future Directions

In addition to educating patients and healthcare practitioners, further steps may be taken to ensure awareness and proper care of irAEs. Wallet cards that detail patients' immunotherapy regimens can help bring an irAE to the attention of an emergency medicine provider and aid in the diagnostic process. The Association of Community Cancer Centers developed an IO Wallet Card (Figure 1, page 41) and made it available as a print-ready PDF at accc-cancer.org/io-walletcard. (Limited print quantities are available. Please contact Janelle Schrag, jschrag@accc-cancer.org for these and other inquiries.) Electronic health record alerts that notify a non-oncology-based provider of patients' immunotherapy regimens could also increase awareness of a possible irAE during an admission. Lastly, an order set specifically designed for the treatment of irAEs could ensure the adequate dosing of corticosteroids and provide options of secondary agents for corticosteroid-refractory situations. OI

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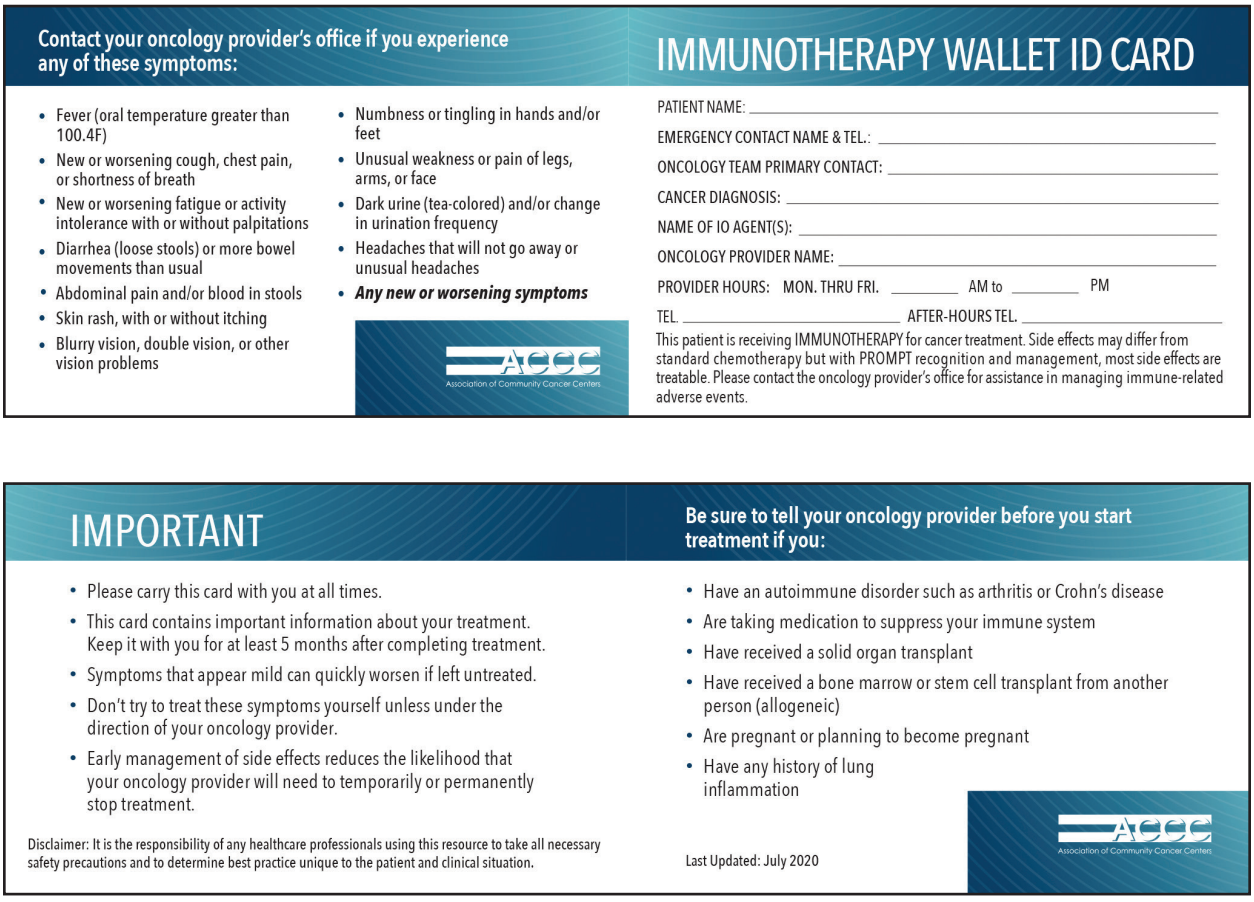
Figure 1. Immunotherapy Wallet ID Card



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