Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center

Imad El Majzoub, MD; Aiham Qdaisat, MD; Kyaw Z. Thein, MD; Myint A. Win, MD; Myat M. Han, MD; Kalen Jacobson, MD; Patrick S. Chaftari, MD; Michael Prejean, RN; Cielito Reyes-Gibby, PhD; Sai-Ching J. Yeung, MD, PhD*

*Corresponding Author. E-mail: syeung@mdanderson.org.

Study objective: Cancer immunotherapy is evolving rapidly and is transforming cancer care. During the last decade, immune checkpoint therapies have been developed to enhance the immune response; however, specific adverse effects related to autoimmunity are increasingly apparent. This study aims to fill the knowledge gap related to the spectrum of immune-related adverse effects among cancer patients visiting emergency departments (EDs).

Methods: We performed a retrospective review of patients treated with immune checkpoint therapy who visited the ED of a comprehensive cancer center between March 1, 2011, and February 29, 2016. Immune-related adverse effects from the ED visits were identified and profiled. We analyzed the association of each immune-related adverse effect with overall survival from the ED visit to death.

Results: We identified 1,026 visits for 628 unique patients; of these, 257 visits (25.0%) were related to one or more immune-related adverse effects. Diarrhea was the most common one leading to an ED visit. The proportions of ED visits associated with diarrhea, hypophysitis, thyroiditis, pancreatitis, or hepatitis varied significantly by immune checkpoint therapy agent. Colitis was significantly associated with better prognosis, whereas pneumonitis was significantly associated with worse survival.

Conclusion: Cancer patients treated with ipilimumab, nivolumab, or pembrolizumab may have a spectrum of immune-related adverse effects that require emergency care. Future studies will need to update this profile as further novel immunotherapeutic agents are added. [Ann Emerg Med. 2019;73:79-87.]

Please see page 80 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2018.04.019

SEE EDITORIAL, P. 88.

INTRODUCTION

Background

Cancer immunotherapy is rapidly evolving and is transforming cancer care.[1] Active research is investigating the development of and emerging results from immune checkpoint therapies, including the most effective treatment duration, the safety and effectiveness of immune checkpoint therapy in selected patient populations, the sequence of therapy in relation to chemotherapy or radiotherapy or targeted therapy, and appropriate combinations of immune checkpoint therapy agents.[2-8]

Cytotoxic T-lymphocyte–associated protein 4 (CTLA4) and programmed cell death protein-1 signaling are involved in the mechanisms by which cancer cells escape surveillance by the immune system, and are the 2 earliest drug targets for immune checkpoint therapy (Figure 1).[9] The first immune checkpoint therapy to be approved by the Food and Drug Administration (FDA) was ipilimumab, which is an antibody against CTLA4.[10] This was followed by the anti–programmed cell death protein-1 antibodies nivolumab and pembrolizumab.[11,12] More recently, antibodies against programmed cell death ligand-1, including atezolizumab, avelumab, and durvalumab, were added to the list of FDA–approved immune checkpoint therapy agents, as was another antibody against CTLA4, tremelimumab. The approved use of immune checkpoint therapy, especially nivolumab, is expanding to many types of malignancies.[13] Because ipilimumab, nivolumab, and pembrolizumab have been in use for a while, the numbers of patients visiting emergency departments (EDs) because of adverse effects from these drugs have increased enough for meaningful statistical analyses.

Editor's Capsule Summary

What is already known on this topic

Immune checkpoint therapies are a rapidly growing approach to cancer treatment. A number of immune-related adverse events have been described.

What question this study addressed

This study describes immune-related adverse events resulting in an emergency department visit at a comprehensive cancer center by patients receiving immune checkpoint therapies (nivolumab, ipilimumab, or pembrolizumab).

What this study adds to our knowledge

Among 1,026 visits, 257 were for immune-related adverse events. The most common adverse events were diarrhea, colitis, dermatitis, pneumonitis, and hypophysitis.

How this is relevant to clinical practice

Emergency physicians providing care for patients receiving immune checkpoint therapies should be aware of the range of possible adverse events from these therapies.

Immune checkpoint therapy–induced immune-related adverse effects are defined as any toxicity with a potential immune-mediated cause. Their management has been reviewed,[14-19] and consensus guidelines for immune-related adverse effect management have been set forth.[15,20,21] However, although acute and delayed immune-related adverse effects relative to the time of treatment are being recognized, long-term or permanent adverse effects are only now beginning to emerge.[19,22,23] Whereas some immune-related adverse effects are associated with rapid onset of morbid and potentially life-threatening symptoms, many immune-related endocrine adverse effects have insidious onset and low-grade nonspecific symptoms, making them difficult to diagnose.[24]

Importance

As the use of immune checkpoint therapies increases, their emerging toxicities present a unique challenge to health care professionals. Patients with cancer who experience acute or subacute onset of symptoms or serious symptoms are likely to seek medical attention in the ED.[25-27] Although the types of problems that cancer patients have when they present to EDs have been profiled[28,29] and the acute management of immune-related adverse effects in the emergency setting has been discussed,[30] the new spectrum of immune-related adverse effects arising from immune checkpoint therapy was not included in these studies. Emergency physicians should be familiar with the distinct adverse-effect profile of immune checkpoint therapy so that they can appropriately and expeditiously diagnose and manage these complications to minimize morbidity and mortality.

Goals of This Investigation

In this report, we summarize the findings from a study of immune checkpoint therapy–induced immune-related adverse effects within the context of emergency care for patients with cancer. Our goals were to profile the immune-related adverse effects of cancer patients visiting the ED after having begun immune checkpoint therapy and to examine the associations between specific immune-related adverse effects and survival to begin filling the knowledge gap related to the spectrum of immune-related adverse effects that patients receiving immune checkpoint therapy experience.

MATERIALS AND METHODS

Study Design and Setting

This retrospective study was conducted under a clinical research protocol approved by the institutional review board of The University of Texas MD Anderson Cancer Center, a comprehensive cancer center located in Houston, TX.

We first reviewed the literature about immune checkpoint therapy–related adverse effects to guide our retrospective study design. The literature review was performed by searching PubMed, MEDLINE, and Google Scholar, using the search terms "immune checkpoint therapy," "emergency," "ipilimumab," "nivolumab," and "pembrolizumab" on January 12, 2018. These anti-CTLA4 and anti–programmed cell death protein-1 agents were the primary immune checkpoint therapies in use for the patient cohort in our study; the anti–programmed cell death ligand-1 agents were only recently developed. Search results were screened for relevance after exclusion of articles in foreign languages, and then reviewed in detail. Particular attention was paid to articles that reported the incidence of immune-related adverse effects (Table 1). Rare adverse effects from case reports also were noted. This literature review guided the data collection about specific immune-related adverse effects in the retrospective review of ED visits.

Selection of Participants

The pharmacy database, which includes both inpatient and outpatient dispensing data for more than 10 years, was

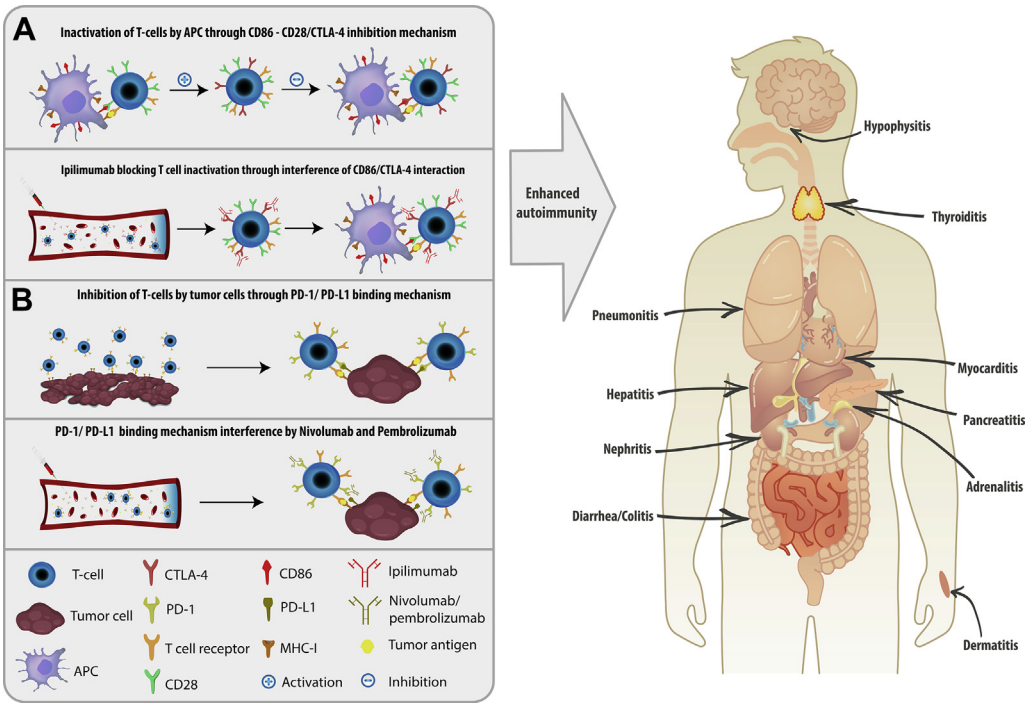

Figure 1. Mechanism and adverse effects of immune checkpoint therapy. Immune checkpoint therapy boosts the immune system's response to cancer cells, providing enhanced T-cell–mediated killing of cancer cells. Left panel, A: Cancer antigens are processed by APCs. T-cells that recognize the cancer antigens are activated by CD86 protein on APCs through binding to CD28 protein. T-cell activation is counterbalanced by inactivation of T-cells through binding of CTLA4 protein to CD86, which results in deactivation of T-cells. Ipilimumab, a monoclonal antibody against CTLA4, interferes with CD86/CTLA4 binding, enhancing the activation of T-cells by APC. Left panel, B: PD-1 cell surface receptor on CD8-positive T-cells allows T-cells to be deactivated. Cancer cells can upregulate expression of PD-L1 to evade attack by the immune system. The use of monoclonal antibody therapy against PD-1, such as nivolumab or pembrolizumab, interferes with PD-L1/PD-1 binding, preventing inactivation of T cells. Right panel: However, enhancement of the immune response to cancer antigens also enhances response to other autoantigens, leading to immune attack of normal tissue and resulting in immune-related adverse effects. *APC*, Antigen-presenting cell; *CD86*, cluster of differentiation 86; *CD28*, cluster of differentiation 28; *PD-L1*, programmed death ligand-1.

queried for a list of patients who had received ipilimumab, nivolumab, or pembrolizumab, either alone or in combination, as shown in Figure 2. The earliest dispensing date for these medications was marked as the initiation of immune checkpoint therapy. This list was then cross-referenced with a list of patients who presented in the MD Anderson ED between March 1, 2011 (1 day after the earliest immune checkpoint therapy initiation date), and February 29, 2016, to identify those who had ED visits subsequent to initiation of immune checkpoint therapy. Exclusion criteria were aged 18 years or younger, and missing emergency physician note.

Data Collection and Processing

Data about immune-related adverse effects identified in the literature search were collected from the patients' electronic medical records (focusing primarily on ED visit notes but also including all subsequent records) by 3 physicians and independently confirmed by 2 physicians in an unblinded manner. Patient demographics, comorbidities, treatments rendered, and subsequent ED visits, which included the visits related to immune-related adverse effects, also were collected.

Outcome Measures

The primary outcome of our study was characterization of the immune-related adverse effects experienced by patients with cancer who reported to the ED after beginning immune checkpoint therapy. The secondary outcome was the association between each identified immune-related adverse effect and overall survival from the ED visit to death. Overall survival was defined as the number of days a patient survived between the date of treatment initiation and the date of death. If patient death could not be verified, survival time was censored at the patient's last confirmed contact with the health care system or at the end of the study period.

Primary Data Analysis

Baseline patient characteristics were analyzed with descriptive statistics (percentages and medians). Percentages of cancer patients with various immune-related adverse effects were tabulated for each immune checkpoint therapy, alone or in combination. Immune-related adverse effects were compared across different immune checkpoint therapy groups. Univariate analysis of the association between individual immune-related adverse effects and overall survival was performed with the Kaplan-Meier method. Multivariate analyses of survival data for all patients were based on Cox proportional hazards modeling; hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). The models were further adjusted for age, sex, race, age-unadjusted Charlson comorbidity index, allergy, and preexisting autoimmune disease. A further subanalysis for patients with no preexisting autoimmune disease was conducted, controlled for the same factors.

Table 1. Summary of literature about the incidence of immune checkpoint therapy–induced immune-related adverse effects.

Literature Reviewed (Year)	Drug Adverse Effect	Total Sample Size Cases Reported, No. (%)	Population
Nivolumab			
Hahn et al (2017)[32]		N=1,994	Incidence of all irAEs (all grade N=1,994) in PD-1 axis inhibitors across clinical trials. Based on studies in medical centers in various countries.
	Hypophysitis	12 (0.6)	
	Colitis	58 (2.9)	
	Pneumonitis	61 (3.1)	
	Nephritis	23 (1.2)	
	Hepatitis	35 (1.8)	
	Dermatitis (rash)	171 (9)	
	Thyroiditis	225 (11.7)	
	T1DM	17 (0.9)	
Webber et al (2015)[33]		N=268	Incidence of all irAEs (all grade N=268). Patients recruited at 90 sites in 14 countries.
	Fatigue	67 (25)	
	Pruritus	43 (16)	
	Diarrhea	30 (11.2)	
	Nausea	25 (9.3)	
	Anemia	12 (5)	
	Decreased appetite	14 (5)	
	Arthralgia	14 (5)	
	Vomiting	9 (3)	
	Constipation	6 (2)	
	Alopecia	1 (0.4)	
Ipilimumab			
Khoja et al (2016)[34]		N=129	A total of 129 patients with metastatic cutaneous melanoma were identified. Princess Margaret Cancer Centre, Canada.
	Diarrhea	34 (26.4)	
	Dermatitis (rash)	18 (14.0)	
	Thyroiditis	8 (6.2)	
	Hypophysitis	6 (4.7)	
	Hepatitis	4 (3.1)	
Bronstein et al (2011)[31]		N=81	Clinical and radiologic manifestations of irAEs in patients with metastatic melanoma who were undergoing anti-CTLA4 antibody therapy. Department of Diagnostic Radiology, MD Anderson Cancer Center.
	Colitis	1 (1.2)	
	Diarrhea	1 (1.2)	
	Dermatitis (rash)	4 (4.9)	
	Hypophysitis	2 (2.5)	
	Uveitis	1 (1.2)	
	Aseptic meningitis	1 (1.2)	
	Arthralgia and myalgia	1 (1.2)	
	Thyroiditis	2 (2.4)	
Pembrolizumab			
Hahn et al (2017)[32]		N=2,799	Incidence of all immune-related adverse events (N=2,799) in PD-1 axis inhibitors across clinical trials. Based on studies in different medical centers in different countries.
	Colitis	48 (1.7)	
	Pneumonitis	94 (3.4)	
	Nephritis	9 (0.3)	
	Thyroiditis	333 (12.4)	
	Hypophysitis	17 (0.6)	
	Hepatitis	19 (0.7)	
	Dermatitis (rash)	39 (1.4)	

Table 1. Continued.

Literature Reviewed (Year)	Drug Adverse Effect	Total Sample Size Cases Reported, No. (%)	Population
Ipilimumab and nivolumab			
Sznol et al (2017)[35]		N=448	Nivolumab and ipilimumab combination therapy in patients with advanced melanoma. Yale Comprehensive Cancer Center.
	Diarrhea	197 (44.0)	
	Colitis	57 (12.7)	
	Pneumonitis	31 (6.9)	
	Thyroiditis	106 (23)	
	Hypophysitis	38 (8.5)	
	Hepatitis	158 (35.3)	
	Fatigue	164 (36.6)	
	Dermatitis (rash)	288 (64.3)	
	Nausea	111 (24.8)	
	Pyrexia	85 (19.0)	
	Decreased appetite	68 (15.2)	
	Vomiting	63 (14.1)	
	Arthralgia	53 (11.8)	
	Increased lipase	55 (12.3)	
	Headache	50 (11.2)	

irAE, Immune-related adverse effects; *PD-1*, programmed death protein 1; *T1DM*, type 1 diabetes mellitus.

Allergy was defined as positive when there were entries to the allergy section of the patient's medical record (excluding seasonal or pollen allergies). Preexisting autoimmune disease was defined as the presence of autoimmune diseases in the medical history (for example, nonsurgical hypothyroidism, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus).

All statistical analyses were performed with R software (version 3.3.3; R Foundation, Vienna, Austria; http://www.r-project.org) and SPSS (version 21; IBM, Armonk, NY).

RESULTS

The prevalence of various immune-related adverse effects caused by nivolumab, pembrolizumab, and ipilimumab has been thoroughly reviewed by others,[31-35] and we have summarized the key reviews (case reports not included) in Table 1. Our data collection process focused on the immune-related adverse effects identified from this literature search: diarrhea,[28] dermatitis[28] (pruritus, rash, dermatitis, erythema, photosensitivity, toxic epidermal necrolysis, urticaria, and vitiligo), colitis,[28] pneumonitis,[28] hypophysitis,[36] pancreatitis,[37] thyroiditis,[38] adrenalitis,[38] nephritis,[32] vasculitis,[39] myocarditis,[40,41] hepatitis,[15,37] and hematologic[42] and ophthalmologic adverse effects.[43]

Characteristics of Study Subjects

During the 5-year study period, 628 patients who received immune checkpoint therapy were identified once the exclusion criteria were applied. These patients made 1,026 visits to our ED after starting immune checkpoint therapy, of which 682 (66.5%) resulted in hospital admission. Approximately one quarter of the 1,026 visits were related to one or more immune-related adverse effects, and among these 257 visits, 210 (81.7%) resulted in admission. Patient demographics and clinical characteristics are summarized in Table 2. Almost half of the study cohort (45.1%) had melanoma, 55.7% had previously known allergies, and 15.8% had a history of autoimmune disease. Of the 628 patients analyzed, 179 (28.5%) were treated with more than one immune checkpoint therapy agent before ED presentation (Figure 2).

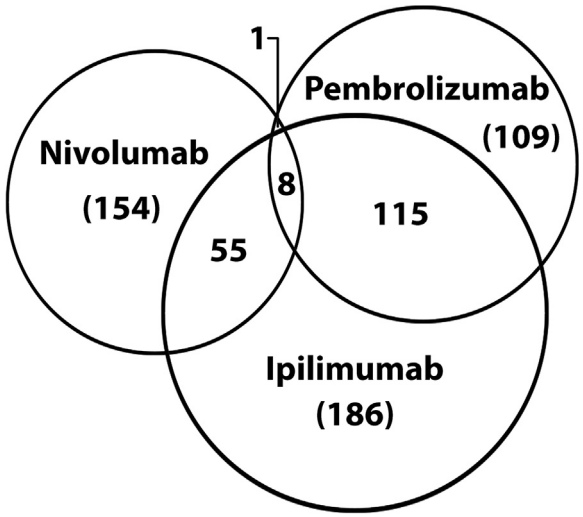

Figure 2. Venn diagram showing the number of patients who visited the ED after initiation of immune checkpoint therapy. The number of patients receiving one treatment is presented in parentheses. The intersection areas represent concurrent or subsequent therapy.

Table 2. Patient demographics and clinical characteristics.

Characteristic	No. of Patients (%)
Total	628
Age, median (range), y	62 (16–86)
Men	389 (61.9)
White	507 (80.7)
Charlson comorbidity index, median (range)	8 (2–15)
Cancer type	
Melanoma	282 (45.1)
Lung cancer	115 (18.4)
Genitourinary cancer	81 (13.0)
Hematologic malignancies	52 (8.3)
Gastrointestinal cancer	37 (5.9)
Head and neck cancer	22 (3.5)
Other solid tumors	36 (5.8)
Preexisting autoimmune disease	99 (15.8)
Allergy	349 (55.7)

Main Results

The numbers and percentages of cancer patients presenting to the ED with various immune-related adverse effects after beginning immune checkpoint therapy were tabulated for each immune checkpoint therapy alone and in combination (Table 3). Diarrhea without the evidence of colitis was the most common immune-related adverse effect, and it appeared to be more commonly associated with ipilimumab (14.5%) and combination immune checkpoint therapy (18.4%) than with nivolumab (8.4%) or pembrolizumab (6.4%), whereas hypophysitis, thyroiditis, and pancreatitis appeared to be more commonly associated with combination immune checkpoint therapy (all 5.0%). Hepatitis was most common in patients treated with nivolumab (6.1%).

Table 3. Adverse effects of immune checkpoint therapy reported by ED patients with cancer.

Adverse Effect	Ipilimumab	Nivolumab	Pembrolizumab	>1 Medication
Total	186 (29.6)	154 (24.5)	109 (17.4)	179 (28.5)
Diarrhea	27 (14.5)	13 (8.4)	7 (6.4)	33(18.4)
Colitis	13 (7.0)	4 (2.6)	2 (1.8)	13 (7.3)
Pneumonitis	6 (3.2)	11 (7.1)	5 (4.6)	8 (4.5)
Dermatitis	8 (4.3)	7 (4.5)	5 (4.6)	14 (7.8)
Hypophysitis	8 (4.3)	1 (0.6)	0	9 (5.0)
Hepatitis	2 (1.1)	11 (6.1)	2 (1.3)	1 (0.9)
Thyroiditis	3 (1.6)	1 (0.6)	0	9 (5.0)
Pancreatitis	2 (1.1)	3 (1.9)	1 (0.9)	9 (5.0)
Adrenalitis	1 (0.5)	2 (1.3)	0	2 (1.1)
Nephritis	0	0	1 (0.9)	1 (0.6)
Hematologic effects	0	0	0	2 (1.1)
Myocarditis	0	0	0	1 (0.6)
Vasculitis	0	1 (0.6)	0	0
Eye effects	0	0	0	1 (0.6)

Data are presented as No. (%).

We investigated whether any of the identified immune-related adverse effects were associated with survival time from the ED visit to death. Kaplan-Meier analysis for each of the main immune-related adverse effects is shown in Figure E1 (available online at http://www.annemergmed.com); univariable and multivariable Cox regression analyses for the overall survival for each immune-related adverse effect are shown in Table 4. Patients who presented with colitis had better overall survival, with HRs of 0.45 (95% CI 0.21 to 0.95) and 0.45 (95% CI 0.21 to 0.98) in the univariable and multivariable models, respectively (Table 4); the HR was 0.49 (95% CI 0.23 to 1.04) when patients with preexisting autoimmune disease were excluded from the analysis. Pneumonitis was associated with poor overall survival, with HRs of 1.64 (95% CI 1.00 to 2.69) and 1.72 (95% CI 1.03 to 2.87) in the univariable and multivariable models, respectively (Table 4). A similar result was observed when patients with preexisting autoimmune disease were excluded in another analysis using a similar multivariable model (HR 1.95; 95% CI 1.09 to 3.47).

LIMITATIONS

Some limitations accompanied our study. Current cancer immunotherapy is still in a state of flux, with rapid changes in the number of agents available, as well as in the approved indications for the existing agents. As the demographics of the patients receiving immune checkpoint therapy change over time, the relative percentages of immune-related adverse effects that require ED visits will also change, which could affect the generalizability of our results. A limitation of our methodology was that the physicians performing the data abstraction were not blinded to the clinical outcomes or the previous abstraction results when performing data confirmation. Given the retrospective nature of our study, using electronic medical records might have resulted in erroneous data, yet the strong medical record system in our institution and the large number of patients included helped in overcoming this limitation. Also, using the last confirmed contact with the health care system when a patient death could not be verified might have resulted in underestimation of the true survival rate. Another limitation of our study is that it involved only one institution, and the sample size is limited. Our findings about the association of colitis with good prognosis and the association of pneumonitis with poor prognosis are interesting but will need to be further investigated and confirmed in different and larger cohorts.

DISCUSSION

Of all the immune-related adverse effects investigated in our study, diarrhea was the most common one associated

Table 4. Univariable and multivariable Cox regression analysis for overall survival for each immune-related adverse effect.

Adverse Effect	Univariable, HR (95% CI)	Multivariable, All Patients (N=628), HR* (95% CI)	Multivariable, Patients Without Preexisting Autoimmune Disease (N=529), HR† (95% CI)
Diarrhea	0.79 (0.53–1.17)	0.80 (0.54–1.20)	0.81 (0.53–1.23)
Colitis	0.45 (0.21–0.95)	0.46 (0.21–0.98)	0.49 (0.23–1.04)
Pneumonitis	1.64 (1.00– 2.69)	1.72 (1.03–2.87)	1.95 (1.09–3.47)
Dermatitis	0.57 (0.29–1.10)	0.60 (0.30–1.17)	0.67 (0.31–1.42)
Hypophysitis	0.54 (0.22–1.30)	0.59 (0.24–1.43)	0.56 (0.21–1.51)
Hepatitis	1.03 (0.42–2.50)	0.91 (0.37–2.24)	1.00 (0.40–2.46)
Thyroiditis	1.01 (0.42–2.46)	1.16 (0.47–2.88)	1.95 (0.78–4.85)
Pancreatitis	0.79 (0.33–1.92)	0.87 (0.36–2.13)	1.05 (0.43–2.60)
Adrenalitis	0.65 (0.16–2.61)	0.72 (0.18–2.96)	0.66 (0.09–4.75)
Myocarditis	4.66 (0.65–33.32)	5.23 (0.70–39.31)	6.05 (0.79–46.07)

*HR adjusted for age, sex, race, Charlson comorbidity index, cancer type, preexisting autoimmune disease, and presence of allergy.
†HR adjusted for age, sex, race, Charlson comorbidity index, cancer type, and presence of allergy.

with ED visits, ranging from 6.4% to 18.4% among different treatment groups. Although hypophysitis is a common immune-related adverse effect in ED visits, its relative prevalence was different among the 4 medication groups in our study (Table 3). ED visits related to hypophysitis appeared to be associated more with combination therapy and ipilimumab than with pembrolizumab or nivolumab. Thyroiditis also was a common immune-related adverse effect among the ED visits, and its relative prevalence was also different among the 4 treatment groups, in a pattern similar to that for hypophysitis. These patterns reflected the previous finding that patients receiving combination therapy are at increased risk for thyroid dysfunction and hypophysitis.[44] Pancreatitis was another immune-related adverse effect for which the relative prevalence differed among the 4 treatment groups (Table 3). ED visits related to pancreatitis appeared to be associated more with combination therapy and nivolumab than with pembrolizumab or ipilimumab. Although myocarditis is a potentially fatal complication of immune checkpoint therapy,[27,44] only one case of (nonfatal) myocarditis was observed, in a patient who visited the ED after receiving more than one immune checkpoint therapy medication. Other identified immune-related adverse effects, such as colitis, pneumonitis, dermatitis, adrenalitis, nephritis, vasculitis, and hematologic and eye adverse effects, were less common in our study and did not show significant differences in proportions among the 4 treatment groups. Overall, the prevalence of the immune-related adverse effects among immune checkpoint therapy–treated cancer patients who visited the ED generally reflected the incidence of immune-related adverse effects in the literature (Table E1, available online at http://www.annemergmed.com).

Pneumonitis is a rare but life-threatening immune-related adverse effect.[22] In our analysis of association with overall survival after the ED visit, pneumonitis was associated with poor survival (HR 1.72; 95% CI 1.03 to 2.87). In contrast, patients who developed colitis had better overall survival, with HR of 0.45 (95% CI 0.21 to 0.98). Therefore, different immune-related adverse effects differentially affected overall survival from the ED visit to death.

The American Society of Clinical Oncology recently published guidelines for management of immune-related adverse effects.[45] In general, immune checkpoint therapy has to be continuously and closely monitored, and emergency physicians should communicate with patients' oncologists about ED visits, diagnoses, and treatments associated with immune-related adverse effects. Grade 1 toxicities that do not affect quality of life can be controlled with topical regimens or oral antipruritics without the use of systemic glucocorticoids. With potentially serious immune-related adverse effects such as neurologic, pulmonary, and cardiac toxicities or grade 3 or 4 toxicities, systemic glucocorticoids (methylprednisolone 1 to 2 mg/kg per day or equivalent) may need to be initiated expeditiously in the ED. Anti–tumor necrosis factor-α therapy may be needed by approximately one third of patients who do not adequately respond to glucocorticoid treatment, even though these medications are rarely needed in the ED setting. Although high-dose glucocorticoids do not appear to compromise the anticancer efficacy of immune checkpoint therapy,[46] the use of high-dose systemic glucocorticoids should be a joint decision between the emergency physician and the oncologist.

In conclusion, our study of immune checkpoint therapy–treated cancer patients who visited the ED

provides an initial glimpse of the spectrum of immune-related adverse effects that emergency clinicians may encounter in the care of cancer patients. This study has highlighted that the most common immune-related adverse effects leading to ED visits were diarrhea, colitis, pneumonitis, hypophysitis, and dermatitis. However, the prevalence of diarrhea, hypophysitis, thyroiditis, and pancreatitis differed significantly among the treatment groups (ipilimumab, pembrolizumab, nivolumab, and combinations of these agents). Pneumonitis is associated with poor prognosis in immune checkpoint therapy–treated cancer patients who visited the ED, and this patient population may demand special attention by emergency physicians.

Given the prevalence of these adverse effects among patients visiting the ED after receiving immune checkpoint therapy, emergency physicians will certainly be faced with the need to identify and manage them. Emergency health care professionals must become familiar with the distinct adverse effects of these agents to be able to recognize and diagnose immune-related adverse effects in a timely manner to minimize the morbidity and mortality that they cause.

The authors acknowledge Jeanie F. Woodruff, BS, ELS, for editorial assistance.

Supervising editor: Timothy F. Platts-Mills, MD, MSc

Author affiliations: From the Department of Emergency Medicine (El Majzoub, Qdaisat, Win, Han, Jacobson, Chaftari, Reyes-Gibby, Yeung), the Division of Nursing (Prejean), and the Department of Endocrine Neoplasia and Hormonal Disorders (Yeung), The University of Texas MD Anderson Cancer Center, Houston, TX; and the Division of Hematology/Oncology, Texas Tech University Health Sciences Center, Lubbock, TX (Thein).

Author contributions: KJ, PSC, CR-G, and S-CJY conceived and designed the study and developed the methods. CR-G and S-CJY provided study supervision. IEM, AQ, KZT, MAW, and MMH conducted chart review. C-RG and S-CJY supervised statistical analysis. IEM, AQ, KZT, MAW, and S-CJY analyzed and interpreted the data. IEM and AQ produced the figures and tables. KJ and MP reviewed the literature. IEM, AQ, and S-CJY drafted the article. All authors contributed substantially to its revision and provided final approval. S-CJY takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be 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.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support grant P30 CA016672. Dr. Yeung is the principal investigator of an investigator-initiated clinical trial supported by DepoMed and a retrospective clinical study supported by Bristol-Myers Squibb through ARISTA-USA (BMS/Pfizer American Thrombosis Investigator Initiated Research Program).

Publication dates: Received for publication January 19, 2018. Revisions received March 26, 2018, and April 5, 2018. Accepted for publication April 16, 2018. Available online June 5, 2018.

Presented at the National Comprehensive Cancer Network 22nd annual conference, Orlando, FL, March 23-24, 2017.

REFERENCES

1. Burugu S, Dancsok AR, Nielsen TO. Emerging targets in cancer immunotherapy. *Semin Cancer Biol*. 2017; https://doi.org/10.1016/j.semcancer.2017.10.001.
2. Balar AV, Weber JS. PD-1 and PD-L1 antibodies in cancer: current status and future directions. *Cancer Immunol Immunother*. 2017;66:551-564.
3. Zhao X, Subramanian S. Oncogenic pathways that affect antitumor immune response and immune checkpoint blockade therapy. *Pharmacol Ther*. 2018;181:76-84.
4. Zhao X, Subramanian S. Intrinsic resistance of solid tumors to immune checkpoint blockade therapy. *Cancer Res*. 2017;77:817-822.
5. Wilson RAM, Evans TRJ, Fraser AR, et al. Immune checkpoint inhibitors: new strategies to checkmate cancer. *Clin Exp Immunol*. 2017;191:133-148.
6. Weichselbaum RR, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol*. 2017;14:365-379.
7. Van Limbergen EJ, De Ruysscher DK, Olivo Pimentel V, et al. Combining radiotherapy with immunotherapy: the past, the present and the future. *Br J Radiol*. 2017;90:20170157.
8. Rotte A, Jin JY, Lemaire V. Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. *Ann Oncol*. 2017; http://doi.org/10.1093/annonc/mdx686.
9. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*. 2015;161:205-214.
10. National Cancer Institute. Ipilimumab. Available at: https://www.cancer.gov/about-cancer/treatment/drugs/ipilimumab. Accessed March 16, 2018.
11. National Cancer Institute. Nivolumab. Available at: https://www.cancer.gov/about-cancer/treatment/drugs/Nivolumab. Accessed March 16, 2018.
12. National Cancer Institute. Pembrolizumab. Available at: https://www.cancer.gov/about-cancer/treatment/drugs/pembrolizumab. Accessed March 16, 2018.
13. Heymach J, Krilov L, Alberg A, et al. Clinical cancer advances 2018: annual report on progress against cancer from the American Society of Clinical Oncology. *J Clin Oncol*. 2018;36:1020-1044.
14. Postow MA. Managing immune checkpoint-blocking antibody side effects. *Am Soc Clin Oncol Educ Book*. 2015; http://doi.org/10.14694/EdBook_AM.2015.35.76.
15. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346-1353.

16. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375-2391.
17. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139-148.
18. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51-60.
19. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168.
20. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95.
21. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev*. 2016;45:7-18.
22. Feld E, Horn L. Emerging role of nivolumab in the management of patients with non-small-cell lung cancer: current data and future perspectives. *Onco Targets Ther*. 2017;10:3697-3708.
23. Cousin S, Seneschal J, Italiano A. Toxicity profiles of immunotherapy. *Pharmacol Ther*. 2018;181:91-100.
24. Sznol M, Postow MA, Davies MJ, et al. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. *Cancer Treat Rev*. 2017;58:70-76.
25. Miller AH, Brock P, Yeung SC. Pituitary dysfunction: a case series of immune checkpoint inhibitor–related hypophysitis in an emergency department. *Ann Emerg Med*. 2016;68:249-250.
26. Win MA, Thein KZ, Qdaisat A, et al. Acute symptomatic hypocalcemia from immune checkpoint therapy–induced hypoparathyroidism. *Am J Emerg Med*. 2017;35:1039.e1035-7.
27. Matson DR, Accola MA, Rehrauer WM, et al. Fatal myocarditis following treatment with the PD-1 inhibitor nivolumab. *J Forensic Sci*. 2017;63:954-957.
28. Mayer DK, Travers D, Wyss A, et al. Why do patients with cancer visit emergency departments? results of a 2008 population study in North Carolina. *J Clin Oncol*. 2011;29:2683-2688.
29. Yang Z, Yang R, Kwak MJ, et al. Oncologic emergencies in a cancer center emergency department and in general emergency departments countywide and nationwide. *PLOS One*. 2018;13:e0191658.
30. Lomax AJ, McNeil C. Acute management of autoimmune toxicity in cancer patients on immunotherapy: common toxicities and the approach for the emergency physician. *Emerg Med Australas*. 2017;29:245-251.
31. Bronstein Y, Ng CS, Hwu P, et al. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *AJR Am J Roentgenol*. 2011;197:W992-W1000.
32. Hahn AW, Gill DM, Agarwal N, et al. PD-1 checkpoint inhibition: toxicities and management. *Urol Oncol*. 2017;35:701-707.
33. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375-384.
34. Khoja L, Atenafu EG, Ye Q, et al. Real-world efficacy, toxicity and clinical management of ipilimumab treatment in metastatic melanoma. *Oncol Lett*. 2016;11:1581-1585.
35. Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. 2017;35:3815-3822.
36. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. *Pituitary*. 2016;19:82-92.
37. Wang W, Lie P, Guo M, et al. Risk of hepatotoxicity in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis of published data. *Int J Cancer*. 2017;141:1018-1028.
38. Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. *Eur J Intern Med*. 2017;47:6-13.
39. Padda A, Schiopu E, Sovich J, et al. Ipilimumab induced digital vasculitis. *J Immunother Cancer*. 2018;6:12.
40. Gibson R, Delaune J, Szady A, et al. Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. *BMJ Case Rep*. 2016; http://doi.org/10.1136/bcr-2016-216228.
41. Laubli H, Balmelli C, Bossard M, et al. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer*. 2015;3:11.
42. Simeone E, Grimaldi AM, Esposito A, et al. Serious haematological toxicity during and after ipilimumab treatment: a case series. *J Med Case Rep*. 2014;8:240.
43. Davis ME, Francis JH. Cancer therapy with checkpoint inhibitors: establishing a role for ophthalmology. *Semin Oncol Nurs*. 2017;33:415-424.
44. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
45. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018; http://doi.org/10.1200/JCO.2017.77.6385.
46. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*. 2015;33:3193-3198.