Demographic Factors Associated with Toxicity in Patients Treated with Anti–Programmed Cell Death-1 Therapy

Kaustav P. Shah[1], Haocan Song[2], Fei Ye[2], Javid J. Moslehi[3], Justin M. Balko[3], Joe-Elie Salem[4], and Douglas B. Johnson[3]

ABSTRACT

Immune checkpoint inhibitors (ICI) are now routinely used in multiple cancers but may induce autoimmune-like side effects known as immune-related adverse events (irAE). Although classical autoimmune diseases have well-known risk factors, including age, gender, and seasonality, the clinical factors that lead to irAEs are not well-defined. To explore these questions, we assessed 455 patients with advanced melanoma treated with ICI at our center and a large pharmacovigilance database (VigiBase). We found that younger age was associated with a similar rate of any irAEs but more frequent severe irAEs and more hospitalizations (OR, 0.97 per year). Paradoxically, however, older patients had more deaths and increased length of stay (LOS) when hospitalized. This was partially due to a distinct toxicity profile: Colitis and hepatitis were more common in younger patients, whereas myocarditis and pneumonitis had an older age distribution both in our center and in VigiBase. This pattern was particularly apparent with combination checkpoint blockade with ipilimumab and nivolumab. We did not find a link between gender or seasonality on development of irAEs in univariate or multivariate analyses, although winter hospitalizations were associated with marginally increased LOS. This study identifies age-specific associations of irAEs.

Introduction

Immune checkpoint inhibitors (ICI) have transformed cancer treatment paradigms, producing durable responses in many patients. However, these agents also trigger immune-related adverse events (irAE) with features mimicking autoimmune disease (1). Clinical or molecular risk factors that lead to irAEs are not well understood, and predicting which patients will be affected is not possible currently. On the other hand, many well-defined risk factors are associated with classical autoimmune conditions including age, environment, family history, and female sex (2). Aging alters immune function (i.e., immune senescence) and is linked with onset of certain autoimmune diseases (e.g., inflammatory bowel disease in younger patients). Gender also appears to play a role, as most (but not all) autoimmune diseases are more common in women (3). Seasonality also correlates with autoimmune disease onset or flares. For example, multiple sclerosis, lupus, and rheumatoid arthritis flares occur more often in the winter, potentially due to vitamin D deficiency or infectious disease patterns (4).

Surprisingly, the effects of even these basic risk factors on irAEs are not well described. Two small studies have shown conflicting data linking age and irAEs, and one study suggested that women were at higher risk of ICI myocarditis, although the effect of gender on other irAEs has not been defined (5–7). Early smaller analyses of gender have also shown conflicting results with one study showing female sex as protective against irAE development and another showing females as more likely to develop irAEs in both melanoma and non–small cell lung cancer (8, 9). Herein, we sought to clarify the effects of age, gender, and seasonality on irAEs in a large cohort of patients with cancer treated with ICI.

Materials and Methods

After obtaining an institutional review board (IRB) waiver of consent from the Vanderbilt University IRB (Nashville, TN, IRB# 161485), we retrospectively reviewed electronic medical records of all consecutive patients with advanced melanoma treated with ICI from one center. All patient studies were conducted in accordance with the U.S. Common Rule after obtaining the IRB waiver of consent. We assessed patient demographics [age, gender, performance status (PS), and comorbid conditions], treatment data (combination PD-1/CTLA-4 blockade vs. anti–PD-1 monotherapy), and toxicity features (including type, severity, hospitalization, and outcome). A logistic regression model assessed risk of (i) any irAE; (ii) severe irAEs [grades 3–5 by Common Terminology Criteria for Adverse Events (CTCAE) v4.03]; and (iii) hospitalization from irAEs, adjusted for age, gender, combination treatment, PS, and season. Seasonality was defined as either season of treatment start or season of toxicity onset. A Poisson regression model analyzed length of stay (LOS) controlled for the above variables.

To validate the findings from the single center, we extracted all cases of myocarditis, colitis, hepatitis, and pneumonitis from ICIs from VigiBase reported through December 2018. VigiBase (http://www.vigiaccess.org/), the World Health Organization database of individual safety case reports, and adverse drug reactions, comprised >17,000,000

[1]Vanderbilt University School of Medicine, Nashville, Tennessee. [2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville Tennessee. [3]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. [4]AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology, Pharmacovigilance Unit, INSERM, UMR ICAN 1166, Sorbonne Universités, UPMC Univ, Paris, France.

Note: Supplementary data for this article are available at Cancer Immunology Research Online (http://cancerimmunolres.aacrjournals.org/).

Corresponding Author: Douglas B. Johnson, Vanderbilt-Ingram Cancer Center, 777 Preston Research Building, Nashville, TN 37232. Phone: 615-875-2179; Fax: 615-343-7602; E-mail: douglas.b.johnson@vumc.org

Cancer Immunol Res 2020;8:851–5

doi: 10.1158/2326-6066.CIR-19-0986

case reports from >130 countries. VigiBase was accessed and queried on December 31, 2018 for myocarditis, autoimmune hepatitis, colitis, and pneumonitis occurring in patients treated with ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab. "Autoimmune hepatitis" was chosen rather than hepatitis or other hepatic toxicities given the diverse causes of hepatic dysfunction in patients with cancer.

Data and statistical analyses

Statistical comparisons were performed using GraphPad Prism version 8.0 and R version 3.6.3. The incidence of all irAEs (defined as any grade using the CTCAE version 4.03), incidence of severe irAEs (CTCAE grades 3–5), and incidence of hospitalization for irAEs were compared between groups using χ^2 analysis. Length of hospitalization was compared between groups using Mann–Whitney U test. Multivariate logistic regression was performed for binary outcomes (incidence of all and severe irAEs, and hospitalizations) and controlled for age, sex, seasonality, PS, and treatment type. Poisson regression was fitted to LOS data, controlling for the same covariates. Missing data in the covariates were completed via multiple imputation using chained equations, assuming missing at random. In VigiBase, the incidence of particular toxicities (colitis, hepatitis, pneumonitis, and myocarditis) was compared between groups using Kruskal–Wallis test. Median age between groups was assessed using Mann–Whitney U test. Two-sided $P < 0.05$ was considered significant.

Results

We identified 455 patients treated with ICI with advanced melanoma from our center. Of these, 287 were men (63%), with median (range) age of 63.0 (18.0–89.0) years. A total of 115 were treated with ipilimumab and nivolumab, and 340 were treated with anti–PD-1 monotherapy. A total of 395 patients (87%) had metastatic disease, whereas 60 (13%) were patients treated in the adjuvant setting. Among all patients, 49.7% ($n = 226$) developed an irAE, 59 patients (13.0%) developed a severe irAE, and 54 patients (11.7%) required hospitalization for irAEs. The most common irAEs were dermatitis (19%), gastrointestinal-related (11%), and endocrine-related events (11%).

Sex was not associated with the rate of development of any irAEs, severe irAEs, or hospitalization in univariate or multivariate analyses (controlled for treatment type, seasonality, age, and PS). Similarly, seasonality (whether measured as season at therapy start or season at worst toxicity) was not associated with irAEs, severe irAEs, or hospitalization. However, when hospitalized, the average LOS for management of an irAE was 6.6 days in the winter compared with 5.9 days in spring, 4.2 days in the summer, and 5.0 days in the fall ($P = 0.006$; summer vs. winter). On multivariate analysis, when adjusted for age, treatment, and gender, LOS differences were not statistically significant ($P = 0.059$; summer vs. winter).

We then assessed the impact of age. Older age was not associated with overall rate of irAEs but associated with decreased severe toxicity rate [OR, 0.97 per year; 95% confidence interval (CI), 0.95–0.99], and need for hospitalization (OR, 0.97; 95% CI, 0.95–0.99) when controlling for gender, PS, season, and combination immunotherapy. Despite this, older patients, when hospitalized, had increased LOS ($P < 0.001$; **Fig. 1**). Three patients with an average age of 68.0 years experienced fatal irAEs, which was higher than the average age of 63.0 for the cohort overall. To assess whether older patients were at greater risk of fatalities when they experienced toxicity, VigiBase was examined. Patients with fatal myocarditis from combination ipilimumab and nivolumab

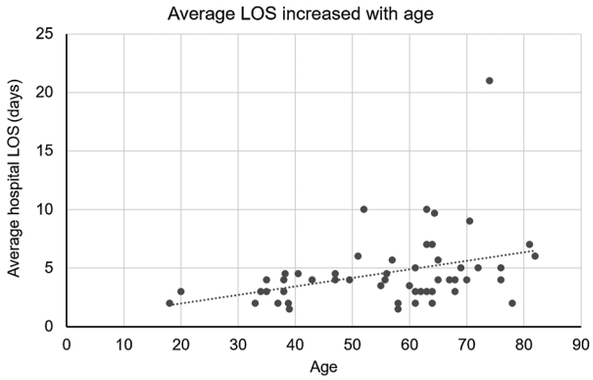

Figure 1.
Relationship of age with LOS for irAE management. Age of patients compared with average LOS in the hospital for irAE management. Each point represents individual patients. Fifty-two patients represented. The dotted line represents the best-fit line for univariate linear regression between LOS and age.

were older than those with nonfatal myocarditis (70.9 vs. 60.7 years; $P = 0.03$), although no age difference between fatal versus nonfatal pneumonitis cases was observed. Thus, paradoxically, younger patients appeared to have more severe irAEs and more hospitalizations, but older patients had increased LOS and increased rate of deaths.

To help elucidate potential explanations for this effect, we hypothesized that specific toxicity types may differ by age. Thus, we queried our institutional 455 patient dataset and stratified patients into four age categories: <45 years, 45–59 years, 60–74 years, and >74 years. Colitis and hepatitis, which are associated with frequent hospitalizations but low death rates (10), were more common in the youngest age subset (16% and 11%, respectively) and decreased in prevalence with increasing age (**Fig. 2A**). In contrast, arthritis and dermatitis, which usually only require outpatient management, occurred increasingly with age ≥60. Seemingly, more heart, muscle, and neurologic events occurred in older patients (5.6% incidence in patients ≥60 vs. 2.7% in patients <60), and pneumonitis also had the highest incidence (8%) in patients over age 75 compared with all other age groups. These were uncommon events but often produced lengthy hospital stays and even mortality. To confirm this finding, we assessed VigiBase. Indeed, among all affected patients, colitis and hepatitis had a substantially younger age distribution compared with myocarditis and pneumonitis (median ages 62, 64, 66, and 69 for hepatitis, colitis, pneumonitis, and myocarditis, respectively; $P < 0.001$; **Fig. 2B**).This relationship held only for combination ipilimumab and nivolumab and ipilimumab monotherapy but not anti–PD-1/PD-L1 monotherapy (**Table 1**; Supplementary Table S1).

We also sought to determine whether medical comorbidities correlated with toxicity. In our center's dataset, the presence of any comorbidity (vs. none) was not associated with risk of toxicity (52% vs. 46%; $P = 0.32$). History of autoimmune disease of any type did not correlate with any toxicity (49% vs. 50%; $P = 0.9$) or severe toxicities (7% vs. 13%; $P = 0.13$). Organ-specific comorbidities, however, could potentially be associated with increased organ toxicities; for example, patients with prior pulmonary comorbidities (chronic obstructive pulmonary disease, sleep apnea, and asthma) had a seemingly higher risk of pneumonitis (13% vs. 6%; $P = 0.06$). Too few patients had preexisting hepatic comorbidities ($n = 13$, of which two developed hepatitis) to make definitive conclusions. Similarly, of the 4 patients with frank myocarditis, 1 had preexisting cardiac disease (coronary artery disease), thus, limiting the ability to assess the relationship of cardiac comorbidities with cardiac toxicity.

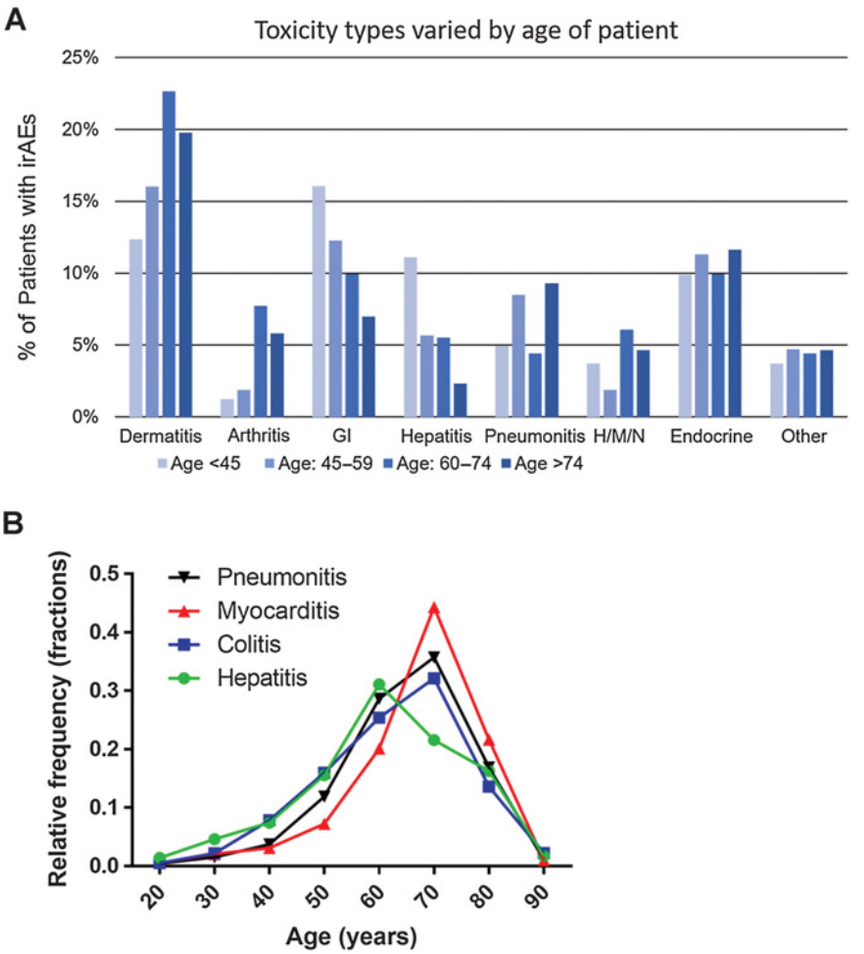

Figure 2.

Relationship between irAE incidence and age. **A,** Incidence of irAEs by specific type of toxicity stratified by age of patients in the single-center analysis. GI, gastrointestinal; H/M/N, heart/muscle/neuro. Age <45, $n = 81$; age 45–59, $n = 106$; age 60–74, $n = 181$; and age >74, $n = 86$. **B,** Incidence of irAEs by age in VigiBase stratified by decade (20: events occurring between 15 and 24.99 years).

Discussion

In this study, we evaluated the impact of several classical autoimmunity risk factors on irAEs. In contrast to autoimmune disease, we did not observe an obvious link between gender or seasonality and irAEs. However, we noted a paradoxical relationship between age and irAEs. Specifically, older age was associated with a similar rate of irAEs,

Table 1. Ages of patients with toxicities in VigiBase[a].

	Toxicity	Number	Median (mean) age	P^b
All cases	Colitis	1,564	64 (62.3)	<0.001
	Hepatitis	283	62 (60.4)	
	Pneumonitis	1,183	66 (64.3)	
	Myocarditis	194	69 (66.4)	
Combination therapy (PD-1 and CTLA-4)	Colitis	296	59.6 (58.8)	<0.001
	Hepatitis	92	56.5 (55.3)	
	Pneumonitis	156	64 (61.3)	
	Myocarditis	41	69 (66.2)	
Ipilimumab therapy	Colitis	732	63.5 (61.8)	0.012
	Hepatitis	48	56.5 (53.9)	
	Pneumonitis	71	60 (61.4)	
	Myocarditis	10	66.3 (60)	
Anti–PD-1/PD-L1 therapy	Colitis	536	67 (64.9)	0.12
	Hepatitis	143	66 (66.0)	
	Pneumonitis	957	66 (65.0)	
	Myocarditis	143	68.1 (66.9)	

[a]Search terms "colitis," "autoimmune hepatitis," "pneumonitis," and "myocarditis."
[b]Kruskal–Wallis test.

overall, and less severe irAEs but longer hospitalizations and more fatalities compared with younger patients. This finding was at least partially explained by distinct types of irAEs across ages, as colitis and hepatitis were more common in younger patients, but arthritis, dermatitis, pneumonitis, and myocarditis occurred more often in older patients.

The mechanisms of irAEs are only beginning to be uncovered. Several provocative studies suggest several potential mechanisms, ranging from shared antigens between tumor and affected tissue, preexisting autoantibodies (and presumably smoldering autoimmunity), and microbial factors (viral or bacterial infection; refs. 11–15). However, identifying clinically useful markers in predicting which patients will be affected has been an elusive goal. Although several studies have suggested that autoantibodies or early-on-treatment B-cell changes may be somewhat predictive, these findings are not yet applicable to clinical practice (16, 17). Still more strikingly, no identified clinical factors that predict toxicity have been identified, as even patients with frank autoimmune disease often do not experience irAEs (18–20).

Although gender and seasonality were not obviously associated with toxicities, age did present a complex relationship with toxicity. This largely appeared because of the distinct types of toxicity observed in different age groups. Some of these distinctions mimicked their non-ICI analogs, as inflammatory arthritis is more common in older patients and inflammatory bowel disease has a younger age-at-onset. One could also speculate that accumulated damage to the lungs or heart (e.g., by smoking or atherosclerotic disease) might predispose older patients to pneumonitis or myocarditis. In our population, PS at time of initiation of immunotherapy treatment did not show a significant association with toxicity. However, this could not be verified in the VigiBase group. Indeed, one retrospective study has implicated diabetes and perhaps preexisting heart disease as a risk factor for myocarditis, although the relationship between smoking and pneumonitis is less clear (21, 22). In our study, patients with any preexisting lung comorbidities had a higher rate of both overall and lung-related irAEs. The sample size was too small to ascertain significance. However, further work should focus on understanding whether patients with prior tissue damage are more susceptible to irAEs. One could also speculate that older patients may be more prone to complications from toxicities or from high-dose steroids, explaining their longer hospitalizations and higher fatality rates.

This study does have some limitations related to the single-center clinical experience, which may be subjected to region-specific biases, and the pharmacovigilance data, which cannot be independently verified. However, the concordant findings between the two distinct datasets lend credence to the findings. Furthermore, we did not assess every possible toxicity, given that certain events, such as rash and arthritis, may be very nonspecific and due to a variety of causes. One limitation for the generalization of these results is that the effect size for differences in both severe toxicity rates and hospitalization rates was small. Ultimately, this study identified distinct toxicity patterns associated with age, which were particularly apparent with combination immunotherapy. A combination of clinical factors, such as age, and molecular biomarkers may help predict which patients will experience irAEs. This study also challenges the current prevailing viewpoint that older patients experience worse toxicities from cancer treatments. Although this is important information, we would not advocate for changing treatment protocols based on age and gender. However, these findings may inform patient selection, monitoring, and treatment.

Disclosure of Potential Conflicts of Interest

J.J. Moslehi is a consultant for Novartis, Bristol-Myers Squibb, Pfizer, AstraZeneca, and Regeneron. J.M. Balko is a consultant/expert witness for Novartis and reports receiving commercial research grants from Genentech, Bristol-Myers Squibb, and Incyte. D.B. Johnson is an advisory board member for Array Biopharma, Bristol-Myers Squibb, Janssen, Merck, and Novartis, and reports receiving commercial research grants from Bristol-Myers Squibb and Incyte. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: K.P. Shah, J.M. Balko, D.B. Johnson
Development of methodology: K.P. Shah, H. Song, J.-E. Salem, D.B. Johnson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.P. Shah, J.-E. Salem, D.B. Johnson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.P. Shah, H. Song, F. Ye, J.-E. Salem, D.B. Johnson
Writing, review, and/or revision of the manuscript: K.P. Shah, F. Ye, J.J. Moslehi, J.M. Balko, J.-E. Salem, D.B. Johnson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.M. Balko, D.B. Johnson

Acknowledgments

This research was supported by NIH grants K23 CA204726 to D.B. Johnson, and R01CA227481 to D.B. Johnson and J.M. Balko.

Received December 16, 2019; revised February 26, 2020; accepted April 23, 2020; published first April 29, 2020.

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