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BRIEF REPORT

The Spectrum of Serious Infections Among Patients Receiving Immune Checkpoint Blockade for the Treatment of Melanoma

Maria Del Castillo,[1] Fabian A. Romero,[2] Esther Argüello,[2] Chrisann Kyi,[3] Michael A. Postow,[2] and Gil Redelman-Sidi[2]

[1]Department of Medicine, Jacobi Medical Center, Bronx; [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, and [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York

The risk of infection among patients receiving immune checkpoint blockade is unknown. We retrospectively reviewed medical records of 740 patients with melanoma who received immune checkpoint blockers. Serious infection occurred in 54 patients (7.3%). The main risk factors were receipt of corticosteroids and/or infliximab.

Keywords. infection; melanoma; checkpoint blockade; immunotherapy.

In the last decade, the development of immune checkpoint-blocking antibodies, such as those directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death receptor 1 (PD-1), and programmed death ligand 1 (PD-L1), has ushered in great promise in the treatment of melanoma and other cancers [1–9]. Several checkpoint inhibitors are now approved by the US Food and Drug Administration for the treatment of melanoma (ie, the CTLA-4 blocking antibody [ipilimumab, Bristol-Myers Squibb], PD-1 blocking antibodies [pembrolizumab, Merck; nivolumab, Bristol-Myers Squibb], and, most recently, the combination of nivolumab plus ipilimumab [1, 2, 10]), and preclinical and clinical data now support the use of these drugs in a rapidly expanding spectrum of malignancies.

Use of immune checkpoint-blocking drugs is associated with a constellation of unique immune-related adverse effects (irAEs) related to the upregulated immune system. These toxicities affect a variety of organ systems including skin (rash), gastrointestinal tract (colitis), pancreas (pancreatitis), liver (hepatitis), endocrine (hypophysitis, thyroiditis), lung (pneumonitis), and kidneys (nephritis) [11, 12]. Immune-related adverse effects are generally reversible when managed according to standard algorithms that make use of immunosuppressive medications such as steroids or, if refractory, tumor necrosis factor alpha (TNF-α) inhibitors (infliximab) [11, 13–15].

Preclinical studies have raised concerns that immune checkpoint blockade is directly associated with increased susceptibility to certain infections, including tuberculosis [16] and listeriosis [17, 18]. A second concern is that susceptibility to infection could increase due to immunosuppression given to treat irAEs related to checkpoint blockade. Indeed, several case reports have been published of opportunistic infections among patients with melanoma receiving the CTLA-4 inhibitor ipilimumab, including invasive aspergillosis, cytomegalovirus-induced hepatitis, and pneumocystis pneumonia (PCP) [19–21]. However, the full extent of infection among patients receiving these novel immunotherapies has not been determined.

Here we describe the spectrum of serious infections and associated risk factors among 740 melanoma patients treated with immune checkpoint inhibitors at Memorial Sloan Kettering Cancer Center (MSKCC).

METHODS

The study was performed at MSKCC (New York, New York), a 471-bed tertiary care cancer center with 19 000 admissions and 122 000 patient-days annually. We retrospectively reviewed the electronic medical records of all patients diagnosed with melanoma and treated with immune checkpoint (CTLA-4, PD-1, and/or PD-L1) blocking agents during a 4-year period from December 2010 to October 2014. Data collected included patient demographics, treatment modality and duration, prior cancer treatments, treatment of irAEs with any immunosuppressive drug, use of antimicrobial prophylaxis, and outcome. We specifically evaluated prior receipt of temozolomide due to its association with prolonged lymphopenia and opportunistic infections [22]. The study was approved by the MSKCC Institutional Review Board.

Infections were identified by reviewing patient laboratory data and imaging studies. For cases with microbiologic and/or radiologic findings suggestive of infection, we further reviewed the clinical medical records to confirm the presence of associated symptoms and ascertain the outcome. Cause of death was determined by agreement between the investigators.

Serious infection was defined as infection requiring hospitalization or parenteral antimicrobials. Serious infection related to immune checkpoint blockade was defined as serious infection occurring at any time from initiation of immune checkpoint blockade till 1 year after its discontinuation. Probable or proven

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Correspondence: G. Redelman-Sidi, Infectious Disease Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (redelmansidi@hotmail.com).

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Table 1. Patient Characteristics and Risk Factors for Serious Infection

Characteristic (n = 740 Patients)	Overall	Serious Infection? Yes (n = 54)	Serious Infection? No (n = 686)	*P* Value	OR (95% CI)
Age, y, mean (range)	63 (4–93)	61.6 ± 2.0	63.0 ± 0.5	.47	
Male sex	469 (63)	40 (74)	430 (63)	.11	1.70 (.90–3.09)
Prior chemotherapy	229 (31)	20 (37)	209 (30)	.36	1.34 (.76–2.39)
Prior temozolomide	142 (19)	12 (22)	130 (19)	.59	1.22 (.64–2.36)
Corticosteroid use	339 (46)	46 (85)	293 (43)	<.0001	7.71 (3.71–16.18)
Infliximab use	54 (7)	13 (24)	41 (6)	<.0001	4.74 (2.27–9.45)

Treatment (n = 898 Treatment Courses)	Overall	Serious Infection? Yes (n = 54)	Serious Infection? Yes (n = 844)	*P* Value	OR (95% CI)
Ipilimumab	658 (73)	40 (74)	618 (73)	.99	1.05 (.55–1.90)
Nivolumab	52 (5.7)	1 (1.9)	51 (6)	.36	0.29 (.03–1.68)
Pembrolizumab	83 (9.2)	0 (0)	83 (9.8)	.0069	0 (0–.63)
Ipilimumab + nivolumab	80 (8.9)	12 (22)	68 (8)	.0017	3.26 (1.70–6.27)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

invasive fungal infection was defined according to published criteria [23]. Receipt of corticosteroids was defined as receipt of an average daily dose of at least 10 mg of prednisone or dose-equivalent corticosteroid for at least 10 days at any time from initiation of immune checkpoint blockade till 1 year after its discontinuation.

Statistical Analysis

Fisher exact test was used to analyze the association between development of infection and categorical variables (sex, use of corticosteroids, use of infliximab, prior temozolomide use, immune checkpoint blockade agent used). The Mann–Whitney test was employed to analyze the association between development of infection and continuous variables (age). A P value $\leq$.05 was considered significant.

RESULTS

During the 4-year study period, 740 patients received 898 courses of immune checkpoint blockade for melanoma at MSKCC. The mean patient age was 63 years; 469 (63%) were men. Two hundred twenty-nine patients (31%) had previously received cytotoxic chemotherapy, including 142 (19%) who had received temozolomide (Table 1).

Monotherapy with a checkpoint-blocking drug was given in 793 (88.3%) courses, including 658 (73.2%) with ipilimumab (CTLA-4 blocker), 52 (5.7%) with nivolumab (PD-1 blocker), and 83 (9.2%) with pembrolizumab (PD-1 blocker). Combination therapy was given in 105 (11.7%) courses, most commonly a combination of ipilimumab and nivolumab in 80 (8.9%), followed by nivolumab and lirilumab in 10 (1.1%). The average treatment course duration was 98 days (range, 1–1309 days).

Three hundred thirty-nine patients (46%) received corticosteroids, of whom 55 (16%) also received infliximab; 1 person was treated with infliximab alone. Other immunosuppressive medications administered included rituximab in 1 patient and mycophenolate-mofetil in 1 patient. The median daily corticosteroid dose (prednisone equivalent) was 40 mg, and the median duration of corticosteroid therapy was 60 days. PCP prophylaxis was given to 144 (42%) of those who received corticosteroids. No other antimicrobial prophylaxis was given.

Serious infection developed in 54 patients (7.3%). The average time from initiation of immune checkpoint blockade to

Table 2. Specific Infection Types

Infection Type	No. of Cases
Bacterial	46
Pneumonia	13
Intra-abdominal infection	7
Craniofacial infection	3
Bacterial bloodstream infection	13
Clostridium difficile–associated diarrhea	10
Fungal	6
Invasive pulmonary aspergillosis	2
Pneumocystis pneumonia	3
Candida bloodstream infection	1
Viral	5
Zoster (disseminated or facial)	3
CMV enterocolitis	1
EBV reactivation causing facial nerve paralysis	1
Parasitic	1
Strongyloides hyperinfection	1
Total[a]	58

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus.

[a] Total number of cases is more than the 54 patients who developed an infection, as some patients developed >1 infection.

development of infection was 135 days (range, 6–491 days). Infection occurred during the first 6 months after initiation of immune checkpoint blockade in 43 of the 54 patients (79.6%). The types of infections that occurred are shown in Table 2. Nine patients (17%) were deemed to have died as a consequence of the infection.

Risk Factors for Serious Infection

A comparison between the patients who developed serious infection and those who did not is shown in Table 1. Factors significantly associated with serious infection were use of corticosteroids (odds ratio [OR], 7.71; 95% confidence interval [CI], 3.71–16.18; $P < .0001$) and use of infliximab (OR, 4.74; 95% CI, 2.27–9.45; $P < .0001$). Use of a combination of ipilimumab and nivolumab was associated with increased risk of serious infection, whereas use of pembrolizumab was inversely associated with development of serious infection. Age, sex, and prior receipt of chemotherapy or temozolomide were not associated with development of serious infection.

DISCUSSION

In this study, we describe the occurrence of serious infections following immune checkpoint blockade in 740 patients with metastatic melanoma. This study is, to our knowledge, the first systematic review of infection among patients receiving immune checkpoint blockade for cancer therapy. We found that the overall incidence of serious infections in this population was 7.3%.

The major risk factor for development of serious infection among these patients was use of immunosuppressive agents, including corticosteroids and infliximab. The risk of serious infection was 13.5% in patients who received either corticosteroids or infliximab but only 2% in those who did not. Our study thus provides a clear definition of the population at risk for infection after immune checkpoint blockade.

We also found that patients receiving a combination of nivolumab and ipilimumab were more likely to have developed serious infection, whereas those who received pembrolizumab were protected. These associations are likely explained by the different incidence of irAEs with each of these treatment regimens. Other researchers have found that patients receiving a combination of nivolumab and ipilimumab had a higher risk for severe irAEs, compared with those receiving ipilimumab alone, and were more likely to require immunosuppressive therapy [2]. Indeed, only 5 of 83 (6%) pembrolizumab-treated patients in our study subsequently received corticosteroids, compared with 55 of 80 (69%) of those treated with nivolumab plus ipilimumab.

As we learn more from patients treated with these novel checkpoint-blocking antibodies, guidelines may be necessary to define the optimal management strategies for irAEs while also minimizing infectious complications. Many of the infections identified in our study could potentially be prevented by use of antimicrobial prophylaxis, but the benefit of such prophylaxis needs to be weighed against the risk of adverse effects and promotion of antibiotic resistance. All 3 patients who developed PCP in our study had not received PCP prophylaxis. We would advocate that PCP prophylaxis be considered in all patients with irAEs who are expected to receive prednisone (or equivalent) for at least 4 weeks, in accordance with published guidelines [24]. The role of antiviral, antibacterial, or antifungal prophylaxis in these patients requires further study, particularly among those at the highest risk. At the minimum, clinicians caring for patients receiving corticosteroids or infliximab for treatment of irAEs should maintain high vigilance for occurrence of symptoms or signs suggestive of infection.

The major strength of our study is the large size of the cohort studied. However, our study also has 2 important limitations. First, the majority of patients in our cohort received ipilimumab alone, thus limiting our ability to generalize our conclusions to patients receiving other drug regimens. Second, our cohort consisted entirely of patients with melanoma. Future studies will be needed to determine whether our conclusions pertain to other populations treated with immune checkpoint blockade, such as patients with non-small-cell or renal-cell carcinoma.

In conclusion, patients with melanoma treated with immune checkpoint blockade have a low risk of developing serious infection, unless they also receive corticosteroids and/or TNF-α inhibitors to treat complications associated with immune checkpoint blockade. Future studies will need to address the best approach to optimize the management of irAEs while also preventing infectious complications among this emerging patient population.

Notes

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