The Impact of Immune Checkpoint Inhibitor-Related Adverse Events and Their Immunosuppressive Treatment on Patients’ Outcomes

Abstract

**Background:** Immune checkpoint inhibitors (ICPIs) are gaining more popularity as a treatment for advanced cancers. However, immune-related adverse events (irAEs) limit their use. We aimed to assess the impact of irAEs and their treatment on clinical and survival outcomes.

**Materials and Methods:** We retrospectively reviewed records of the patients who received ICPIs between 2011 and 2017. Descriptive analyses were employed to compare different groups. Kaplan–Meier curves and log-rank tests were used to estimate and compare overall survival durations. **Results:** Of 427 identified patients, 202 (47.3%) had one or more irAEs. Overall, the patients who developed irAEs had better overall survival than did patients with no-irAEs, regardless of immunosuppressant treatment ($P < 0.01$). Patients with mild irAEs who did not require immunosuppressive treatment had longer overall survival duration than did patients without irAEs ($P < 0.01$). Patients with three or more irAEs had longer median overall survival compared to patients with two or less irAEs ($P = 0.01$). Infliximab was associated with shorter duration of steroid use as compared to steroid treatment only (2 months [standard deviation (SD), 8] vs. 4 months [SD, 4]). Steroid treatment for >30 days was associated with higher rate of infections compared to shorter duration ($P = 0.03$). **Conclusion:** IrAEs are associated with favorable overall survival, regardless of immunosuppression treatment requirement. IrAEs involving multiple organs appeared to be beneficial for overall survival. Early infliximab use shortens the duration of steroid treatment and therefore balances better cancer outcomes with decreased risk of infection.

**Keywords:** Adverse events, immune checkpoint inhibitor, immunosuppressive treatment, immunotherapy, impact, survival, toxicities

Introduction

Immune checkpoint inhibitors (ICPIs) have been a treatment option for patients with advanced cancers since the first agent, ipilimumab, was approved for clinical use by the United States Food and Drug Administration in 2011. ICPIs destroy tumor cells by inhibiting proteins that allow tumor cells to evade detection by T-cells, including programmed death protein 1 (PD-1), PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thereby reactivating cytotoxic T-cells. ICPIs have been proven to significantly improve overall survival and delay tumor progression in patients with melanoma, nonsmall cell lung cancer, and other types of cancers.

Despite the success of these drugs, ICPI treatment still has challenges and limitations. Immune-related adverse events (irAEs) require early recognition and prompt treatment. IrAEs can involve a wide variety of organs, most commonly the skin, gastrointestinal (GI) tract, liver, lung, and endocrine system, and can cause moderate symptoms or severe complications and even death. GI tract toxicities, including diarrhea and colitis, are the second most common irAEs. Therefore, a detailed understanding of the characteristics of GI tract irAEs is essential.

Because irAEs are autoimmune, immunosuppression with steroids is commonly the first-line treatment. For patients whose symptoms respond inadequately or don't respond to steroid therapy to steroid therapy and those who suffer severe steroid-related adverse events, other immunosuppressive agents are used, such as the tumor necrosis factor-alpha inhibitor infliximab. With appropriate and timely treatment, most irAEs can be substantially reversed.

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Researchers continue to debate whether the occurrence of irAEs is an indicator of favorable tumor response to ICPI treatment.\(^{[15,16]}\) However, lengthy immunosuppressive treatment may hamper the enhancing effect of ICPI treatment on patients’ immune systems, weakening the immune attack on the tumor, and raising the risk of infection. These contradictory effects should be taken into account when managing irAEs with immunosuppressive treatment. Definitive evidence regarding the association of irAEs, complications related to immunosuppressive treatment of irAEs, and tumor response to ICPIs is lacking as is the evidence for how irAEs affect overall survival.

In this retrospective study, we aimed to describe the characteristics and treatment of patients at a tertiary-care cancer center who developed irAEs following anti-PD-1/PD-L1, anti-CTLA-4, or combination ICPI therapy for solid and hematological malignancies. We also aimed to determine the impact of various patient- and ICPI-related factors, including the characteristics of irAEs, on overall survival.

**Materials and Methods**

**Study design and population**

This retrospective, descriptive, single-center study was conducted with approval from the Institutional Review Board at The University of Texas MD Anderson Cancer Center. Included patients (1) were 18 years of age or older, (2) had an established diagnosis of solid or hematological malignancy, and (3) received single- or multiple-agent ICPI therapy between March 2011 and March 2017.

**Data collection**

Patient information and data relating to ICPI treatment and irAEs were extracted from electronic medical records and our institutional pharmacy database. We collected information on patient demographics, medical history, cancer-related variables, ICPI regimen(s), irAEs, irAE treatment, infectious adverse events related to irAE treatment, and the date of death or last contact. Patient demographics consisted of age, sex, and race/ethnicity. Variables pertaining to medical history included concomitant morbidities, lifetime smoking history, and nonsteroidal anti-inflammatory drug (NSAID) use within 3 months of ICPI initiation. Concomitant morbidities were recorded from a review of medical records, diagnostic laboratory studies, and histopathology reports. Reported comorbidities included hypertension, diabetes mellitus, dyslipidemia, hypocortisolism, chronic obstructive pulmonary disease, asthma, coronary artery disease, congestive heart failure, atrial fibrillation, HIV infection, GI graft versus host disease, and autoimmune diseases (celiac disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, connective tissue disease, sarcoidosis, Sjögren’s syndrome, and Hashimoto thyroiditis).

Oncological details collected included the type, site, and stage of cancer. Cancer type was categorized as hematological malignancy, melanoma, or solid tumor. Because melanoma was the only skin malignancy reported, we considered melanoma instead of skin tumor as a distinct category. The stage of melanoma and solid tumors was reported according to the American Joint Committee on Cancer staging system 7\(^{th}\) edition.\(^{[17]}\) The stage of hematological malignancies was not reported. ICPIs used included ipilimumab, nivolumab, pembrolizumab, and atezolizumab. The ICPI regimen was classified as “combination” if the patient received both nivolumab and ipilimumab during the same treatment course. Overall survival duration was measured from the time of first ICPI dose to the time of death or last clinical encounter for patients who were still alive.

IrAEs were categorized on the basis of the involved organ(s) as diarrhea/colitis, hepatitis, pneumonitis, endocrine dysfunction, dermatitis, and anemia. The number of organs involved was recorded for each patient. The grade of diarrhea and colitis, determined using the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.03, was extracted from the electronic medical records at the time of initial presentation. For non-GI irAEs, only events of Grade 2 or higher were recorded. The immunosuppressive agent(s) used for the treatment of irAEs were steroids and infliximab. In our study population, the symptoms of all the patients who received infliximab were refractory to steroid treatment; therefore, all patients who received infliximab also received steroids. The duration of steroid treatment was measured from the time of steroid therapy initiation at the time of irAE diagnosis to the cessation of steroid treatment or return to the previous baseline dosage received as part of the cancer treatment regimen. In addition, we categorized the duration of steroid treatment as “long” if it was >30 days or “short” if it was 30 days or fewer. Information on infections that occurred at any time from the beginning of steroid treatment through 1 month after the discontinuation of immunosuppressive treatment was extracted from medical records and diagnostic laboratory studies. We categorized types of infection on the basis of the organ involved and/or the inciting organism.

**Statistical analysis**

Statistical analysis was performed using SPSS Statistics software (version 24.0; IBM Corporation, Armonk, NY, USA). We summarized the distribution of the data using descriptive statistics: means and standard deviations for continuous variables; frequencies and percentages for categorical variables. Continuous variables were compared using the Wilcoxon ranked-sum test. The Fisher’s exact test or the Chi-square test was conducted to evaluate associations between categorical variables. Multivariate logistic regression analysis was performed to assess for
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Independent associations between factors found to be significant in the univariate analysis and the development of irAE(s) or infection. Kaplan–Meier curves were used to estimate unadjusted overall survival durations. Log-rank tests were used to compare overall survival durations between groups. All statistical tests were two-sided. P < 0.05 was considered statistically significant.

Results

Patient population

A total of 427 patients were included in this analysis between March 2011 and March 2017. Among them, 202 patients had either single or multiple irAEs, and 225 patients had no irAE. A total of 117 (27.4%) patients had ICPI-related diarrhea and/or colitis.

Immune-related adverse events

Clinical characteristics of patients who had irAEs and those who did not have irAEs are compared in Table 1. Patients with irAEs received ICPI treatment for shorter duration than did patients without irAEs (81 days vs. 112 days, P = 0.018). No differences were found between the two groups in age, sex, smoking history, concomitant autoimmune disease, multiple comorbidities, NSAID, or immunosuppressant use within 3 months of ICPI initiation.

A single irAE occurred in 126/202 (62.4%) patients, and multiple irAEs occurred in 76/202 (37.6%) patients [Table 2]. Diarrhea/colitis was observed in 64/126 (50.8%) patients as a single irAE and in 53/76 (69.7%) patients as one of the multiple irAEs. Pneumonitis was the most commonly reported non-GI irAE (n = 42, 20.8%). The type of immunosuppressive treatment, duration of treatment, and rate of associated infections were comparable between the single- and multiple-irAE groups.

Immunosuppressive treatment for immune-related adverse events

Among patients who developed irAEs, 145 (71.8%) needed immunosuppressive treatment [Table 3]. Steroid monotherapy was used to treat 108 (74.5%) of these patients, and steroid + infliximab combination was used to treat 37 (25.5%) patients. Patients with melanoma were treated significantly more often with a steroid + infliximab combination than with steroid monotherapy (P < 0.001). However, steroid monotherapy was used to treat patients with Stage IV malignancies significantly more often than was the steroid + infliximab combination (89.0% vs. 67.6%; P = 0.005). Steroid monotherapy was administered for a longer mean duration than was the steroid + infliximab combination although the difference was not statistically significant (4 months vs. 2 months; P = 0.198). The number of infection events was higher in patients who received steroid monotherapy (n = 50, 46.3%) than in patients who received steroid + infliximab combination (n = 13, 35.1%); however, again, the difference was not significant (P = 0.256).

Cancer type

Ipilimumab was used to treat melanoma more frequently than other cancers (melanoma, 70.3% vs. hematological malignancies, 20.9% and solid tumors, 30.0%; P < 0.001). No significant difference in the mean duration of ICPI treatment was observed between patients with different cancer types. IrAEs were significantly more common and required more often treatment with steroid + infliximab in patients with melanoma than in those with other cancers (both P < 0.001). The mean duration of

Table 1: Demographic and clinical characteristics of patients with and without immune checkpoint inhibitor-related adverse events

| Characteristic               | irAE (s)       | No irAE        | P     |
|-----------------------------|---------------|---------------|-------|
| Mean age in years (SD)      | 61.2 (13)     | 59.1 (14)     | 0.120 |
| Male sex, n (%)             | 133 (65.8)    | 142 (63.1)    | 0.613 |
| Race/ethnicity, n (%)       |               |               |       |
| White                       | 178 (88.1)    | 164 (72.9)    | <0.001|
| Other                       | 24 (11.9)     | 61 (27.1)     |       |
| NSAID use, n (%)            | 84 (41.6)     | 87 (38.7)     | 0.554 |
| Smoking, n (%)              | 92 (45.5)     | 112 (49.8)    | 0.385 |
| Autoimmune disease, n (%)   | 7 (3.5)       | 15 (6.7)      | 0.188 |
| Multiple comorbidities, n (%)| 56 (27.7)     | 69 (30.7)     | 0.524 |
| Cancer type, n (%)          | 85 (42.1)     | 53 (23.6)     | <0.001|
| Melanoma                    | 47 (23.3)     | 29 (12.9)     |       |
| Head, neck, and chest       | 28 (13.9)     | 67 (29.8)     |       |
| Other solid tumors          | 14 (6.9)      | 18 (8.0)      |       |
| Leukemia and myelodysplastic syndrome | 9 (4.5) | 28 (12.4) |       |
| Lymphoma                    | 14 (6.9)      | 19 (8.4)      |       |
| Multiple myeloma            | 5 (2.5)       | 6 (2.7)       |       |
| Cancer stagea, n (%)        |               |               |       |
| III                         | 28 (13.9)     | 8 (3.6)       | <0.001|
| IV                          | 146 (72.3)    | 159 (70.7)    |       |
| ICPI, n (%)                 |               |               |       |
| Ipilimumab                  | 103 (51.0)    | 73 (32.4)     | <0.001|
| Nivolumab                   | 50 (24.8)     | 91 (40.4)     |       |
| Pembrolizumab               | 29 (14.4)     | 55 (24.4)     |       |
| Combinationb                | 19 (9.4)      | 6 (2.7)       |       |
| Atezolizumab                | 1 (0.5)       | 0 (0.0)       |       |
| ICPI duration in days, mean (SD) | 81 (119) | 112 (149) | 0.018 |

*American Joint Committee on Cancer staging system; includes only solid tumors. Combination: Ipilimumab + nivolumab. ICPI: Immune checkpoint inhibitor, irAE: Immune-related adverse event, SD: Standard deviation, NSAID: Nonsteroidal anti-inflammatory drug
steroid treatment did not differ significantly by cancer type ($P = 0.218$), but more patients with melanoma and solid tumors received long duration steroid treatment than did patients with hematological malignancies ($P < 0.001$). Significantly more patients with melanoma (19.6%) and solid tumors (15.3%) developed infections than did patients with hematological malignancies (5.8%; $P < 0.001$).

The mean duration of ICPI treatment was longer for patients with Stage IV cancers than for those with Stage III disease although the significance level was marginal (101 days vs. 58 days; $P = 0.072$). A higher proportion of patients with Stage III cancer developed irAEs than did patients with Stage IV cancer ($P = 0.001$). Moreover, irAEs in patients with Stage III cancers were more likely to be refractory to steroid treatment and to require infliximab treatment than were irAEs in patients with Stage IV disease ($P < 0.001$). Significantly more patients with Stage III cancer received a long course of steroid treatment than did patients with Stage IV cancer ($P = 0.005$).

### Number of involved organs

In general, we found no significant differences between patients with single or multiple irAEs requiring immunosuppressive treatment [Table 4]. Diarrhea/colitis was the most common irAE requiring immunosuppressive treatment in both groups. The mean duration of ICPI treatment before the onset of the first irAE was similar: 78 days for patients with a single irAE and 62 days for patients with multiple irAEs ($P = 0.414$). Steroid monotherapy was used more often than steroid + infliximab to treat both single and multiple irAEs, and the mean duration of steroid treatment was comparable in both groups ($P = 0.129$). Most patients with both single and multiple irAEs received a long course (>30 days) of steroid treatment. The number of infection events was also comparable in patients with single and multiple irAEs requiring immunosuppressive treatment ($P = 0.653$).

### Table 3: Clinical characteristics of patients receiving steroid monotherapy or combination steroid + infliximab to treat immune checkpoint inhibitors-related adverse events

| Characteristic | Steroid only ($n=108$) | Steroid and infliximab ($n=37$) | $P$ |
|----------------|------------------------|---------------------------------|-----|
| Cancer type, $n$ (%) | | | |
| Solid tumors | 57 (52.8) | 8 (21.6) | <0.001 |
| Melanoma | 43 (39.8) | 29 (78.4) | |
| Hematological malignancies | 8 (7.4) | 0 | |
| Cancer stage, $n$ (%) | | | |
| Stage III | 11 (11.0) | 12 (32.4) | 0.005 |
| Stage IV | 89 (89.0) | 25 (67.6) | |
| Duration of ICPI use in days, mean (SD) | | | |
| Colitis grade, $n$ (%) | | | |
| 1 | 20 (46.5) | 10 (28.6) | 0.160 |
| 2–3 | 24 (53.5) | 25 (71.4) | |
| Diarrhea grade, $n$ (%) | | | |
| 1 | 12 (27.9) | 1 (2.9) | 0.004 |
| 2–4 | 32 (72.1) | 34 (97.1) | |
| Number of organs involved, $n$ (%) | | | |
| 1 | 70 (64.8) | 25 (67.6) | 0.330 |
| 2 | 29 (26.9) | 7 (18.9) | |
| 3 | 8 (7.4) | 3 (8.1) | |
| 4 | 1 (0.9) | 1 (2.7) | |
| 5 | 0 | 1 (2.7) | |
| Duration of steroid use in months, mean (SD) | | | |
| Infectious events, $n$ (%) | | | |
| 1 | 70 (64.8) | 25 (67.6) | 0.330 |
| 2 | 29 (26.9) | 7 (18.9) | |
| 3 | 8 (7.4) | 3 (8.1) | |
| 4 | 1 (0.9) | 1 (2.7) | |
| 5 | 0 | 1 (2.7) | |

*American Joint Committee on Cancer staging system; 8 patients with hematological malignancies had no staging information. *Colitis and diarrhea were graded in 79 patients according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.03. *Infectious events occurring from the time of immunosuppressive treatment initiation to 1 month after treatment completion were recorded. ICPI: Immune checkpoint inhibitor

**Table 2: Characteristics of immune checkpoint inhibitors-related adverse events in patients with single and multiple immune checkpoint inhibitors-related adverse events**

| Characteristic | Patients with single irAE ($n=126$) | Patients with multiple irAEs ($n=76$) | $P$ |
|----------------|-------------------------------------|--------------------------------------|-----|
| Adverse event, $n$ (%) | | | |
| Diarrhea/colitis | 64 (50.8) | 53 (69.7) | |
| Pneumonitis | 16 (12.7) | 26 (34.2) | |
| Endocrine | 9 (7.1) | 30 (39.5) | |
| Dermatitis | 14 (11.1) | 24 (31.6) | |
| Hepatitis | 10 (7.9) | 25 (32.9) | |
| Anemia | 1 (0.8) | 12 (15.8) | |
| Other | 12 (9.5) | 10 (13.2) | |
| Grade of diarrhea, $n$ (%) | | | |
| 1 | 10 (15.6) | 20 (37.7) | 0.052 |
| 2 | 18 (28.1) | 13 (24.5) | |
| 3–4 | 36 (56.3) | 20 (37.8) | |
| Steroid, $n$ (%) | 70 (55.6) | 38 (50.0) | 0.472 |
| Steroid + infliximab, $n$ (%) | 25 (19.8) | 12 (15.8) | 0.574 |
| Adverse event treatment, $n$ (%) | | | |
| Long-duration steroid* | 60 (47.6) | 36 (47.4) | 0.204 |
| Short-duration steroid* | 35 (27.8) | 14 (18.4) | |
| No treatment | 31 (24.6) | 26 (34.2) | |
| Infectious events*, $n$ (%) | 39 (31.0) | 24 (31.6) | 0.256 |

*Long-duration steroid use: >30 days, *Short-duration steroid use: ≤30 days, *Infectious events occurring from the time of immunosuppressive treatment initiation to 1 month after treatment completion were recorded. irAE: immune-related adverse event, ICPI: Immune checkpoint inhibitor.
Immune checkpoint inhibitor type

The mean duration of ICPI treatment was significantly shorter for regimens containing ipilimumab than for nivolumab alone or pembrolizumab alone ($P = 0.001$) [Table 5]. Overall, patients who received regimens containing ipilimumab developed significantly more irAEs than did patients who received single-agent nivolumab or pembrolizumab ($P < 0.001$). GI tract irAEs were the most common irAEs in patients who received regimens containing ipilimumab (41.8%) or pembrolizumab (22.6%), whereas pneumonitis was more common in patients who received single-agent nivolumab (14.9%). The proportion of GI tract irAEs was higher in patients who received regimens containing ipilimumab or pembrolizumab than in patients who received single-agent nivolumab ($P < 0.001$). Immunosuppressive treatment with steroids alone or in combination with infliximab was more frequently used in patients who received regimens containing ipilimumab than in those who received other agents ($P = 0.043$ and $P < 0.001$, respectively). Infections were more frequently reported in patients receiving regimens containing ipilimumab than in patients receiving single-agent nivolumab or pembrolizumab ($P = 0.001$).

Factors associated with the risk of developing immune-related adverse events

The results of multivariate logistic regression analysis to identify independent risk factors associated with irAE regardless of the need for immunosuppressive treatment are shown in Table 6. White patients had a higher risk of irAEs than did other patients (odds ratio [OR], 2.69; 95% confidence interval [CI], 1.49–2.69; $P = 0.001$). Cancer Stage III was associated with an increased risk of irAEs (OR, 5.26; 95% CI, 2.08–12.25; $P < 0.001$). Patients with melanoma had an increased risk of irAEs (OR, 2.33; 95% CI, 1.18–4.59; $P = 0.015$). The risk of irAEs was also higher in patients receiving ipilimumab as a monotherapy or in combination with nivolumab than in patients receiving other ICPIs (OR, 2.33; 95% CI, 1.31–4.16; $P = 0.004$). The duration of ICPI treatment did not affect the risk of irAEs ($P = 1.000$).

Infectious adverse events associated with immunosuppression

In patients who received immunosuppressive treatment, 63 infectious adverse events were recorded. The most common type of immunosuppression-related infection was pneumonia ($n = 18$, 29%). Immunosuppressive treatment was complicated by the development of bacteremia or sepsis in 6 (10%) patients. Patients who received a short course ($\leq$30 days) of steroid treatment had a significantly lower infection rate (30.4%) than did patients who received a long course of steroids (50.0%; $P = 0.033$) [Figure 1a]. Moreover, patients treated with a short course of a steroid + infliximab combination experienced a much lower rate of infection (18.7%) than did patients treated with a long course of steroid monotherapy (50.7%; $P = 0.026$) [Figure 1b]. Multivariate logistic regression analysis demonstrated that the duration of steroid use was associated with an independent risk of infection events related to immunosuppression (OR, 1.22; 95% CI, 1.05–1.41; $P = 0.010$) [Table 7]. Age, cancer type, number of irAEs, and infliximab use were not associated with infection events.

Overall survival estimates

The median length of follow-up was 15 months. Kaplan–Meier curves demonstrated that the duration of steroid use was associated with an independent risk of infection events related to immunosuppression (OR, 1.22; 95% CI, 1.05–1.41; $P = 0.010$) [Table 7]. Age, cancer type, number of irAEs, and infliximab use were not associated with infection events.
Table 5: Patient clinical characteristics by immune checkpoint inhibitor

| Characteristic                          | Ipilimumab/combination (n=201) | Nivolumab (n=141) | Pembrolizumab (n=84) | P       |
|----------------------------------------|---------------------------------|-------------------|----------------------|---------|
| Mean duration of ICPI use in days (SD) | 71 (110)                        | 117 (161)         | 128 (138)            | 0.001   |
| Adverse event type, n (%)              |                                 |                   |                      |         |
| Diarrhea/colitis                       | 84 (41.8)                       | 13 (9.2)          | 19 (22.6)            |         |
| Hepatitis                              | 24 (11.9)                       | 7 (5.0)           | 4 (4.8)              |         |
| Pneumonitis                            | 17 (8.5)                        | 21 (14.9)         | 4 (4.8)              |         |
| Endocrine                              | 25 (12.4)                       | 12 (8.5)          | 2 (2.4)              |         |
| Dermatitis                             | 25 (12.4)                       | 11 (7.8)          | 2 (2.4)              |         |
| Anemia                                 | 8 (4.0)                         | 4 (2.8)           | 1 (1.2)              |         |
| Other                                  | 12 (6.0)                        | 7 (5.0)           | 5 (6.0)              |         |
| Number of organs involved, n (%)       |                                 |                   |                      |         |
| 1                                      | 70 (34.8)                       | 34 (24.1)         | 21 (25.0)            | <0.001  |
| >1                                     | 52 (25.9)                       | 16 (11.3)         | 8 (9.5)              |         |
| None                                   | 79 (39.3)                       | 91 (64.5)         | 55 (65.5)            |         |
| Colitis grade b, n (%)                 |                                 |                   |                      |         |
| 1                                      | 21 (35.0)                       | 2 (40.0)          | 6 (46.2)             | 0.746   |
| 2–3                                    | 39 (65.0)                       | 3 (60.0)          | 7 (53.8)             |         |
| Diarrhea grade b, n (%)                |                                 |                   |                      |         |
| 1                                      | 10 (16.7)                       | 1 (20.0)          | 2 (15.4)             | 0.973   |
| 2–4                                    | 50 (83.3)                       | 4 (80.0)          | 11 (84.6)            |         |
| irAE treatment, n (%)                  |                                 |                   |                      |         |
| Steroid                                | 61 (30.3)                       | 33 (23.4)         | 14 (16.7)            | 0.043   |
| Steroid + infliximab                   | 27 (13.4)                       | 2 (1.4)           | 7 (8.3)              | <0.001  |
| Mean duration of steroid use in months (SD) | 4 (8.8)                    | 2.7 (2.4)         | 2.5 (4.5)            | 0.537   |
| Adverse event treatment, n (%)         |                                 |                   |                      |         |
| Long-duration steroid d                 | 58 (28.9)                       | 23 (16.3)         | 14 (16.7)            | 0.002   |
| Short-duration steroid d                | 30 (14.9)                       | 12 (8.5)          | 7 (8.3)              |         |
| Infectious events, n (%)               | 35 (17.4)                       | 17 (12.1)         | 10 (11.9)            | 0.001   |

\*Combination: Ipilimumab + nivolumab.
\*Colitis and diarrhea were graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.03.
\*Long-duration steroid use: >30 days,
\*Short-duration steroid use: ≤30 days,
\*Infectious events occurring from the time of immunosuppressive treatment initiation to 1 month after treatment completion were recorded.

ICPI: Immune checkpoint inhibitor, SD: Standard deviation, irAE: immune-related adverse event

Table 6: Multivariate logistic regression for immune checkpoint inhibitors-related adverse events risk

| Characteristic                          | irAE risk         | P       |
|----------------------------------------|-------------------|---------|
| Race (white)                           | 2.69 (1.49–2.69)  | 0.001   |
| Cancer stage III                       | 5.26 (2.08–12.50) | <0.001  |
| Cancer type                            |                   |         |
| Melanoma                               | 2.33 (1.8–4.59)   | 0.015   |
| Solid tumors                           | 1.66 (0.90–3.08)  | 0.103   |
| ICPI                                   |                   |         |
| Ipilimumab or combination              | 2.33 (1.31–4.16)  | 0.004   |
| Nivolumab                              | 1.05 (0.56–1.97)  | 0.885   |
| Pembrolizumab                          | Reference         |         |
| Duration of ICPI treatment             | 0.26 (0.99–1.00)  | 1.000   |

ICPI: Immune checkpoint inhibitor, irAE: immune-related adverse event, OR: odds ratio, CI: Confidence interval

Table 7: Multivariate logistic regression model showing association of patient characteristics with risk of infection related to immunosuppressant use

| Characteristic                          | Infection riska   | P       |
|----------------------------------------|-------------------|---------|
| Age at time of ICPI initiation         | 1.00 (0.97–1.03)  | 0.953   |
| Cancer type                            |                   |         |
| Melanoma                               | 0.33 (0.04–2.52)  | 0.286   |
| Solid tumors                           | 0.37 (0.06–2.43)  | 0.302   |
| ICPI                                   |                   |         |
| Ipilimumab or combination              | 0.59 (0.21–1.68)  | 0.325   |
| Nivolumab                              | 0.74 (0.21–2.67)  | 0.646   |
| Number of irAEs                        |                   |         |
| Multiple                               | 1.18 (0.54–2.58)  | 0.681   |
| Infliximab use                         | 0.78 (0.32–0.89)  | 0.582   |
| Duration of steroid treatment          | 1.22 (1.05–1.41)  | 0.010   |

\*Combination: Ipilimumab + nivolumab. ICPI: Immune checkpoint inhibitor, irAE: immune-related adverse event, OR: Odds ratio, CI: Confidence interval

outcomes between patients with one irAE and those with two irAEs (P = 0.764) [Figure 3b].
Furthermore, patients with irAEs that required immunosuppressive treatment had longer median overall survival than did patients without irAEs \((P < 0.001)\) [Figure 4a]. However, when only patients with irAEs were compared, immunosuppressive treatment did not affect survival durations \((P = 0.726)\) [Figure 4b]. The median overall survival duration in patients who received steroid + infliximab combination was comparable to that in patients who received steroid monotherapy \((P = 0.455)\) [Figure 4c]. Patients with a single GI tract irAE had significantly longer overall survival than did those with a single non-GI tract irAE \((P = 0.029)\) [Figure 5]. Survival analysis for patients with melanoma and solid tumors revealed that patients with Stage III cancer had longer overall survival than did patients with Stage
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IV disease although the statistical significance of this difference was marginal ($P = 0.051$) [Figure 6a]. In patients with irAEs, patients with Stage III cancers were not found to have longer overall survival than patients with Stage IV cancer ($P = 0.132$) [Figure 6b]. However, among patients with Stage IV cancer, the median overall survival duration of patients with irAEs was longer than that of patients without irAEs ($P < 0.001$) [Figure 6c]. In patients with

Figure 3: Kaplan–Meier curves comparing overall survival estimates by number of immune-related adverse events. (a) One or two immune-related adverse events versus three or more immune-related adverse events. (b) One immune-related adverse event versus two immune-related adverse events.

Figure 4: Kaplan–Meier curves comparing overall survival estimates by immune-related adverse event treatment. (a) Immune-related adverse event requiring immunosuppressive treatment versus no immune-related adverse event. (b) Immune-related adverse events with treatment versus immune-related adverse events without treatment. (c) Steroid monotherapy versus steroid + infliximab.
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Figure 5: Kaplan–Meier curve comparing overall survival estimates by organ affected by immune-related adverse event (gastrointestinal versus nongastrointestinal).

malignancies, the occurrence of irAE was associated with better overall survival ($P = 0.004$) [Figure 6d]. Likewise, in patients with solid tumors, irAEs were predictors of longer survival duration ($P = 0.005$) [Figure 6e]. However, in patients with hematological malignancies, the survival difference was not significant between patients with irAE versus non-irAE ($P = 0.347$) [Figure 6f]. For patients with Stage IV melanoma, irAE independently predicted better overall survival ($P = 0.007$) [Figure 6g].

Discussion

This is by far the largest-scale study with long-term follow-up conducted in a single center focusing on adverse events related to ICPI use in patients with solid or hematological malignancies. We found that patients who developed irAEs had longer overall survival durations than did patients who did not develop irAE(s), irrespective of the need for immunosuppressive treatment and the number of organs involved. In addition, we observed that steroid treatment for > 30 days was associated with a significantly increased rate of infection. Our findings corroborate those of previous studies conducted in patients with melanoma and nonsmall cell lung cancer although the definitive effect of irAEs on patients’ long-term cancer outcomes is still under debate.\cite{15,18-24} The data from our large sample size study were quite convincing regarding the remarkable impact of irAEs on overall survival duration.

We also reported that ipilimumab triggered more irAEs than other ICPIs, which is in concordance with other studies’ results.\cite{25-27} This may explain why the median duration of ipilimumab treatment was shorter than that of other ICPIs. We recorded cancer stage only for solid tumors and melanomas because the staging systems used for hematological malignancies vary widely and cannot easily be correlated with solid tumor staging.

We found that even though many patients developed multiple irAEs, immunosuppressive treatment was not administered more often in patients with multiple irAEs than in those with single irAE. Diarrhea/colitis was the most common irAE observed in our patient population. Multiple irAEs could develop simultaneously or within a short period, which would be covered by a single complete course of immunosuppressive treatment or sequentially which would require a longer course of immunosuppressive treatment.

Overall, more patients with solid tumors and melanoma developed irAEs than did patients with hematological malignancies, likely to because ICPIs were used to treat these types of cancers earlier than they were used to treat hematological malignancies. The finding of increased risk of irAEs associated with Stage III cancer is anticipated. One of the reasons behind this observation is that patients with Stage III cancer received higher dose of CTLA-4 (10 mg/kg), as approved for clinical use, compared to patients with Stage IV cancer (3 mg/kg). Another reason is that PD-1 as monotherapy is approved for the treatment of patients with Stage IV cancer but not Stage III cancer. Furthermore, we speculate that the greater tumor burden of advanced, Stage IV cancers with their distant spread and extensive involvement could have mitigated the effect of ICPI treatment.

We found that patients with irAEs had longer overall survival duration than did patients without irAEs. This finding could have been a result of aggregating patients with various cancer types and stages that have variable disease courses as well as prognosis. With these potential confounding factors in mind, additional comparisons were conducted by stratifying patients according to cancer type and stage. Findings yielded from such stratification of our cohort were in concordance with our initial verdict of longer overall survival duration in all but one subset of patients, those with hematological malignancies. This could have been due to an underpowered analysis and should be taken into consideration by investigators while designing the future studies. These observations support our conclusion that irAE occurrence is a consistent independent predictor of longer survival regardless of cancer stage.

As immunosuppressive agents are currently the mainstay of treatment for irAEs, adverse events related to immunosuppressive treatment, especially infection, are a concern. Not surprisingly, we observed a significantly higher number of infections in patients treated with a steroid for > 30 days than in patients treated for 30 or fewer days. We compared the rates of infection in patients who received the two extremes of immunosuppressive treatment – a long course of steroids without infliximab or a short course of steroids with infliximab – and found that the difference became even more apparent. Indeed, the length of steroid treatment was the only independent factor that increased the risk of infection. These results provide clear guidance
Figure 6: Kaplan–Meier curves comparing overall survival estimates in patients with solid tumors or melanoma by cancer stage and immune-related adverse event occurrence. (a) All patients, cancer Stage III versus Stage 4. (b) Patients with immune-related adverse event, cancer Stage III versus Stage IV. (c) Patients with Stage IV cancer: Immune-related adverse event versus no immune-related adverse event. (d) Patients with melanoma: immune-related adverse event versus no immune-related adverse event. (e) Patients with solid tumors: immune-related adverse event versus no immune-related adverse event. (f) Patients with hematological malignancy: immune-related adverse event versus no immune-related adverse event. (g) Patients with stage IV melanoma: immune-related adverse event versus no immune-related adverse event.
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to balance the favorable effects on outcomes associated with
irAEs against the need to minimize the risk of infection by
introducing infliximab quickly when irAEs occur.
We detected significantly better survival outcomes in
patients who developed irAE (s) than in those who
did not, regardless of the need for immunosuppressive
agents. Even patients who had only mild irAEs that did
not require immunosuppressive treatment still had better
outcomes than patients who did not have irAEs at all. This
observation is distinctive to our analysis; most previous
studies focused mainly on patients with irAEs that required
treatment with immunosuppressants. Moreover, the need
for, type and duration did not affect long-term survival
in patients who developed irAEs. These findings suggest
that immunosuppressive treatment is safe and does not
compromise the favorable outcomes of ICPI treatment that
are thought to be associated with irAEs.

We specifically compared the overall survival duration of
patients with GI tract irAEs to that of patients with irAEs
involving other organs and interestingly found that patients
with GI tract irAEs had longer overall survival. However,
we did not collect details about the grade of non-GI tract
irAEs, so it is unclear whether this finding can be explained
by differences in the severity of irAEs in the GI tract and
other organs, although our sample size should have had
enough power for this comparison. In addition, we found
that patients with three or more irAEs had better outcomes
than those with two or fewer irAEs. We suspect that not
only the presence of an irAE, but also the higher level of
severity associated with more extensive organ involvement,
can predict a better long-term outcome.

There are some limitations to our study. First, because
we included patients with many different cancer types to
optimize our sample size, variation in the stage, disease
characteristics, and course of different cancers could
have confounded our results, particularly the overall
survival analyses. Second, owing to the complexity of
the criteria for evaluating progression-free survival, we
did not analyze this outcome. Third, the treatment of
irAEs with immunosuppression was mainly based on the
general clinical condition of the patient, at the discretion
of the primary treating physician, which could be different
according to the standard practice of different departments.

Conclusion
Taken together, our study showed that irAE is an
independent predictor for a better overall survival,
irrespective of the need for immunosuppressive treatment
or number of organs involved. Multiple organ involvement
was associated with overall favorable survival. Our results
suggest that early introduction of nonsteroidal
immunosuppressive drugs such as infliximab can reduce
the duration of steroid treatment in patients with irAEs,
thereby balancing better cancer outcomes and a decreased
risk of infection. Future prospective studies are required to
thoroughly elucidate the association between risk factors
for ICPI-induced multiorgan toxicities, tumor response to
ICPIs, and long-term survival.

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