Toxicity, disease management and outcome of treatment with immune checkpoint inhibitors by sex in patients with cancer and preexisting autoimmune disease

MICHAEL LIU[1], LISA CHRIST[2], ANKE RICHTERS[3,4] and BERNA C. ÖZDEMIR[1]

Departments of [1]Medical Oncology, and [2]Rheumatology and Immunology, Inselspital Bern, Bern University Hospital, University of Bern, CH-3011 Bern, Switzerland; [3]Department of Research and Development, The Netherlands Comprehensive Cancer Organisation, 3511 DT Utrecht; [4]Radboud University Medical Center, Radboud Institute for Health Sciences, 6525 GA Nijmegen, The Netherlands

Received February 13, 2023; Accepted June 9, 2023

DOI: 10.3892/ol.2023.13963

Abstract. Female sex is associated with a higher risk for autoimmune diseases (ADs) and immune-related adverse events (irAEs) from immune checkpoint inhibitors (ICIs). While the safety of ICIs in AD cohorts has been reported, sex-segregated data on patient characteristics and outcomes are lacking. In the present study, the disease and treatment characteristics of 51 patients with cancer and preexisting AD (PAD) treated with ICIs at Bern University Hospital Cancer Center (Bern, Switzerland) between January 2017 and June 2021 were analyzed by sex. Rheumatic (n=12/27, 44.4%) and endocrine (n=11/24, 45.8%) PADs were most common among male and female patients, respectively. At the time of ICI initiation, 29.6% (n=8/27) of male and 20.8% (n=5/24) of female patients received immunosuppression for their PAD. Female patients were more likely to experience an irAE (58.3 vs. 48.1%), and less likely to encounter an exacerbation of their PAD (38.5 vs. 14.3%) compared with male patients. Multiple-site irAEs (46.2 vs. 21.4%), implication of an organ specialist for irAEs (100.0 vs. 57.1%) and use of additional immunosuppressive drugs (38.4 vs. 7.7%) were more common in male patients. IrAEs were resolved and ICIs were discontinued in 69.2% (n=9/13) and 71.4% (n=10/14) of the total male and female patients, respectively. Median progression-free survival was higher in male than female patients with irAEs (19.9 vs. 10.7 months) and without irAEs (4.4 vs. 1.8 months). The median overall survival time was higher in male than female patients with irAEs (not estimable vs. 22.5 months) and without irAEs (10.1 vs. 7.4 months). Taken together, these results suggested that sex-related differences existed regarding the clinical presentation of irAEs and treatment outcome.

Correspondence to: Dr Berna C. Özdemir, Department of Medical Oncology, Inselspital Bern, Bern University Hospital, University of Bern, Freiburgstrasse 18, CH-3011 Bern, Switzerland
E-mail: berna.oezdemir@insel.ch

Key words: autoimmune disease, cancer, immune checkpoint inhibitors, safety, toxicity, survival, immune-related adverse events, sex

Introduction

Dysfunctional immunity is linked to autoimmune diseases (ADs) and cancer. Preexisting autoimmune diseases (PADs) are found in ~10% of patients with cancer (1,2). Immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) axis alone or in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors have rapidly become a standard of care for various cancer types, with an increasing number of new indications since their introduction in oncology in 2011 (3). Physiologically, inhibitory receptors, such as CTLA-4, PD-1 and lymphocyte-activation gene 3, are induced upon T-cell activation to limit immune responses after antigen encounter (4). ICI therapy abrogates the inhibition of antitumor immunity by these checkpoints. However, the extent and duration of ICI treatment-induced immune activation varies and can result in immune-related adverse events (irAEs). Most irAEs are low-grade according to the Common Terminology Criteria for Adverse Events (5) and self-limiting. IrAEs can potentially affect any organ system, cause irreversible damage, be high-grade and require immunosuppressive treatment in a subset of patients (6). The risk of severe grade 3-4 irAEs is higher for anti-CTLA4 treatment (range, 28-58%) depending on the dose (7,8), alone or in combination with anti-PD1 (59%) (8) compared with anti-PD1 monotherapies (range, 10-15%) (9,10). Notably, treatment-related mortalities can occur in 0.4-1.2% of patients (11).

The pathogenesis of irAEs is not fully understood, but several mechanisms have been proposed. Autoreactive T-cells due to shared antigens with tumor cells, increased production of inflammatory cytokines by activation of the Th1 and Th17 pathway (for example, in colitis), antibody-dependent cellular toxicity induced by ectopic expression of CTLA-4 (for example, in hypophysitis) or modulation of antibody production by B-cells by tumor-reactive T-cells may contribute to irAEs (12-14).

Given the increased risk of T-cell activity against antigens present in healthy tissues and the close resemblance of irAEs to AD, patients with PAD have been excluded from initial ICI trials due to fear of the exacerbation of PAD and an increased risk of high-grade irAEs (15). The prevalence of PAD is higher among patients with cancer (11.3-13.5%) (2,16) compared with the general population (5%) (17).

Meanwhile, real-world data on the outcome and safety of ICI treatment in patients with cancer with PAD has been reported, yet without considering patient sex as a notable risk determinant of ADs and irAEs. The incidence of most ADs is ≤10-fold higher in the female population, and female sex is associated with a higher risk for experiencing irAEs (17,18). Moreover, symptom severity, disease course, treatment response and overall survival (OS) of AD differs between male and female patients. These differences may be related to sex hormones, chromosomes and differences in the composition of the gut microbiome (17). Additionally, environmental estrogens present in cosmetics and care products have been suggested to have an impact on the immune system (17). Despite these clinically relevant differences, sex-segregated data on toxicity, management and outcome of patients with cancer and PAD receiving ICIs are lacking.

The objective of the present study was to describe the occurrence of irAEs in male and female patients with cancer with PAD receiving ICI treatment and to study the association with survival outcomes.

Patients and methods

Study population. A retrospective cohort study of consecutive patients was performed. Medical records from Bern University Hospital Cancer Center (Bern, Switzerland) were used to identify patients with the following eligibility criteria: i) ≥18 years old; ii) administration of ≥1 cycle of ICI therapy between January 2017 and June 2021; and iii) presence of ≥1 PAD. PAD was defined as an autoimmune disease diagnosed prior to the start of ICI therapy. Patients not fulfilling all criteria were excluded from the analysis. The American Joint Committee on Cancer classification (8th edition) was used as the staging system (19). Information about every identified patient was documented, including sex, age at treatment start, cancer type, time of initiation of ICI therapy, type of ICI administered, line of ICI and best radiological response to treatment.

Regarding PAD and irAEs, the following data were collected: i) type of PAD; ii) activity of PAD at the time of ICI start; iii) exacerbation of PAD after ICI start; iv) incidence; and v) treatment of new all grade irAEs, and consultation of an organ specialist for irAE management after ICI start. PADs were categorized as rheumatic, endocrine, dermatological, gastrointestinal or other irAEs comprising neuromuscular and hematological disorders based on the involved organ systems. It was possible that every patient could have ≥1 PAD. Exacerbation was defined as worsening of the underlying PAD due to an irAE. IrAEs were defined as of a single site if the patient experienced only one type of irAE, or as of multiple sites if the patient experienced irAEs of different types (for example, rheumatic, endocrine, dermatological or gastrointestinal). The incidence of irAEs in patients with cancer treated at Bern University Hospital Cancer Center has previously been reported (18). Data were collected in August 2022 and included until last available follow-up or death. The current study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Commission of the Canton of Bern (approval no. 2021-01335; Bern, Switzerland).

Statistical analysis. Patient, tumor and treatment characteristics were compared using Fisher's test and the χ^2-test. Progression-free survival (PFS) and OS were illustrated using Kaplan-Meier curves and compared using log-rank tests. Patients who did not have an event (neither progression nor mortality in case of PFS; no mortality in case of OS) at the cut-off date were censored. The median follow-up duration was calculated by reverse Kaplan-Meier. Responses were evaluated using the Response Evaluation Criteria In Solid Tumors criteria (version 1.1) (20) according to local clinical practice. Statistical analyses were performed using R (version 4.2.2; https://www.r-project.org/).

Results

Patient characteristics. A total of 689 consecutive patients with cancer who received ≥1 dose of ICI treatment were identified (18). Of those, 51 (7.4%) patients had a concomitant PAD and were included in the population of the present study. Patient characteristics were analyzed by sex (Table I). There were more male than female patients (n=27/51, 52.9%). The median age at the time of ICI treatment start was 69 years (range, 46-81) for male patients and 63 years (range, 37-83) for female patients. The most frequent cancer type, independent of sex, was lung cancer, including non-small cell lung cancer, small cell lung cancer, mesothelioma and pleomorphic lung cancer (n=25/51, 49.0%), followed by melanoma (n=11/51, 21.6%). Other cancer types included urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, Hodgkin lymphoma and mycosis fungoides. Most male and female patients had stage IV disease (63.0 and 83.3%, respectively). Stage III was more common in male than female patients (33.3 vs. 12.5%). In total, ~25% of all patients had brain metastases, independent of sex.

The most applied ICI was pembrolizumab (n=21/51, 41.2%) regardless of the patient sex, followed by nivolumab (n=7/24, 29.2%) in female patients, and ipilimumab in combination with nivolumab in male patients (n=5/27, 18.5%).

In total, 44.4% of male patients had a preexisting rheumatological disease (n=12/27), while endocrine disorders affected 45.8% of the female patients (n=11/24). Other types of PAD were more common in female patients (n=4/24, 16.7%) and included demyelinating polyradiculopathy (1 male patient), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-receptor encephalitis (1 female patient), multiple sclerosis (1 female patient), autoimmune hemophilia (1 female patient) and polyglandular autoimmune syndrome (1 female patient). PAD types are listed in Table I.

At ICI initiation, PAD was in remission and required either topical or systemic immunosuppression in 29.6% of male (n=8/27) and 20.8% of female (n=5/24) patients, respectively.

Incidence and outcome of irAEs, and exacerbation of PAD during ICI treatment. In total, 24 irAEs were detected in

Table I. Characteristics of 51 patients with cancer and PAD.

Patient and treatment characteristics	Male (n=27)	Female (n=24)
Median age (range), years	69 (46-81)	63 (37-83)
Cancer type, n (%)		
Lung cancer	12 (44.4)	13 (54.2)
Melanoma	6 (22.2)	5 (20.8)
Gastrointestinal cancer	2 (7.4)	1 (4.2)
Renal cell carcinoma	1 (3.7)	2 (8.3)
Head and neck cancer	1 (3.7)	0 (0.0)
Breast cancer	0 (0.0)	3 (12.5)
Other	5 (18.5)	0 (0.0)
Cancer stage, n (%)		
III	9 (33.3)	3 (12.5)
IV	17 (63.0)	20 (83.3)
Other	1 (3.7)	1 (4.2)
Presence of brain metastases, n (%)		
Yes	7 (25.9)	6 (25.0)
No	20 (74.1)	18 (75.0)
ICI received, n (%)		
Pembrolizumab	11 (40.7)	10 (41.7)
Ipilimumab + nivolumab	5 (18.5)	4 (16.7)
Nivolumab	4 (14.8)	7 (29.2)
Atezolizumab	2 (7.4)	3 (12.5)
Durvalumab	4 (14.8)	0 (0.0)
Avelumab	1 (3.7)	0 (0.0)
Treatment line, n (%)		
Neoadjuvant	0 (0.0)	1 (4.2)
Adjuvant	4 (14.8)	1 (4.2)
First line	16 (59.3)	15 (62.5)
Second or further line	7 (25.9)	7 (29.2)
Type of PAD, n (%)		
Rheumatological	12 (44.4)	7 (29.2)
Polyarthritis	6	4
Connective tissue disease	1	0
Vasculitis	2	0
Polymyalgia rheumatica	3	3
Endocrine	8 (29.6)	11 (45.8)
Idiopathic hypothyroidism	4	5
Hashimoto thyroiditis	2	3
Autoimmune hyperthyroidism	1	3
Polyglandular autoimmune syndrome	0	1
Dermatological	7 (25.9)	4 (16.7)
Psoriasis	6	3
Cutaneous lupus erythematosus	0	1
Bullous dermatitis	1	0
Gastrointestinal	3 (11.1)	2 (8.3)
Ulcerative colitis	3	1
Crohn's disease	0	1
Other	1 (3.7)	4 (16.7)
Activity of PAD at the time of ICI, n (%)		
In remission without immunosuppression	19 (70.4)	19 (79.2)
In remission with immunosuppression, topical or systemic	8 (29.6)	5 (20.8)

ICI, immune checkpoint inhibitor; PAD, pre-existing autoimmune disease.

Table II. Incidence and outcome of irAEs and exacerbation of PAD under ICI in 51 patients.

Patient characteristics	Male (n=27)	Female (n=24)	P-value
irAEs, n (%)			0.47[a]
Yes	13 (48.1)	14 (58.3)	
No	14 (51.9)	10 (41.7)	
New onset irAEs, n (%)	8 (61.5)	12 (85.7)	0.21[b]
Exacerbation of PAD, n (%)	5 (38.5)	2 (14.3)	
Type of irAEs (multiple per patient possible), n (%)	24 (88.9, 24/27)	18 (75.0, 18/24)	0.58[b]
Arthritis	5 (20.8, 5/24)	1 (5.6, 1/18)	
Colitis	4 (16.7, 4/24)	3 (16.7, 3/18)	
Thyroiditis	3 (12.5, 3/24)	3 (16.7, 3/18)	
Dermatitis	3 (12.5, 3/24)	2 (11.1, 2/18)	
Hepatitis	2 (8.3, 2/24)	5 (27.8, 5/18)	
Pneumonitis	2 (8.3, 2/24)	1 (5.6, 1/18)	
Adrenalitis	1 (4.2, 1/24)	2 (11.1, 2/18)	
Other	4 (16.7, 4/24)	1 (5.6, 1/18)	
Single site irAEs, n (%)	7 (53.8)	11 (78.5)	0.24[b]
Multiple site irAEs, n (%)	6 (46.2)	3 (21.4)	
Median time to onset of irAEs from start of ICI, days (range)	62 (22-698)	66.5 (3-538)	0.40[c]
Implication of organ specialist upon irAEs, n (%)			0.01[b]
Yes	13 (100.0)	8 (57.1)	
No	0 (0.0)	6 (42.9)	
Treatment of irAEs, n (%)			0.31[b]
None	1 (7.7)	2 (14.3)	
ICI interruption	1 (7.7)	0 (0.0)	
ICI de-escalation	0 (0.0)	2 (14.3)	
Corticosteroid treatment	11 (84.6)	10 (71.4)	
Topical	2 (18.2)	0 (0.0)	
Systemic	9 (81.8)	10 (100.0)	
Other immunosuppressive drugs	5 (38.5)	1 (7.1)	
Methotrexate	3 (60.0)	0 (0.0)	
Infliximab	0 (0.0)	1 (100.0)	
Mycophenolate mofetil	1 (20.0)	0 (0.0)	
Mesazalin	1 (20.0)	0 (0.0)	
Other treatments	3 (23.1)	1 (7.1)	
Local corticosteroid infiltration	1 (33.3)	1 (100.0)	
Filgrastim	1 (33.3)	0 (0.0)	
NSAIDs	1 (33.3)	0 (0.0)	
Outcome of irAEs, n (%)			0.35[b]
Resolved, ICI discontinued	9 (69.2)	10 (71.4)	
Resolved, ICI de-escalated	0 (0.0)	2 (14.3)	
Resolved, ICI continued	2 (15.4)	2 (14.3)	
Ongoing at data cut-off or mortality, ICI discontinued	2 (15.4)	0 (0.0)	
Best response, n (%)			0.52[b]
Complete remission	3 (11.1)	2 (8.3)	
Partial remission	14 (51.9)	7 (29.2)	
Stable disease	3 (11.1)	5 (20.8)	
Progressive disease	6 (22.2)	8 (33.3)	
Mixed response	0 (0.0)	1 (4.2)	
Not available	1 (3.7)	1 (4.2)	

[a]χ^2 test. [b]Fisher's test. [c]Log-rank test. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NSAID, non-steroidal anti-inflammatory drugs; PAD, preexisting autoimmune disease.

Table III. Characteristics of patients experiencing PAD exacerbation.

Patient no.	Sex	Age, years	Cancer type	ICI	Type of PAD	Time to exacerbation, days	Treatment of exacerbation	Outcome of exacerbation	Course of ICI after exacerbation	Best response	PFS time, days
1	M	77	Melanoma	Nivolumab + ipilimumab	Rheumatoid arthritis	59	Systemic cortisone, MTX, local infiltration	Resolved	ICI discontinued	PR	250
2	M	67	NSCLC	Durvalumab	Rheumatoid arthritis	22	Systemic cortisone, MTX	Resolved	ICI discontinued	PR	268
3	M	66	NSCLC	Pembrolizumab	Psoriatic arthritis	600	Systemic cortisone, MTX, NSAIDs	Resolved	ICI discontinued	PR	873
4	M	71	NSCLC	Nivolumab	Ulcerative colitis	56	Topical cortisone, topical mesalazin	Resolved	ICI discontinued	PD	55
5	M	66	NSCLC	Durvalumab	Basedow's disease	79	ICI interruption	Resolved	ICI discontinued	PR	542
6	F	61	NSCLC	Pembrolizumab	Hashimoto thyroiditis	70	ICI interruption	Resolved	ICI discontinued	PR	232
7	F	60	Melanoma	Nivolumab	Crohn's disease	56	Systemic cortisone, infliximab	Resolved	ICI discontinued	PR	832

PAD, preexisting autoimmune disorder; M, male; F, female; ICI, immune checkpoint inhibitor; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; PD, progressive disease; PFS, progression-free survival; PR, partial response; NSCLC, non-small cell lung cancer.

13 male patients (n=13/27, 48.1%) compared with 18 irAEs detected in 14 female patients (n=14/24, 58.3%) (Table II). The majority of these were new onset irAEs not related to PAD in either sex. It was revealed that 38.5% (n=5/13) of the male patients experiencing irAEs had an exacerbation of their PAD compared with 14.3% (n=2/14) of the female patients with irAEs (Table III).

The type of irAEs differed by sex. Arthritis (n=5, 20.8%), colitis (n=4, 16.7%) and others, including aplastic anemia, vasculitis, nephritis, pancreatitis and keratitis were the most frequent irAEs in male patients. Hepatitis (n=5, 27.8%), colitis (n=3, 16.7%) and thyroiditis (n=3, 16.7%) were the most common irAEs in female patients. Male patients were more likely to report irAEs affecting multiple organ sites (46.2%, n=6/13 vs. 21.4%, n=3/14). The median time to irAEs was similar: 62 days (range, 22-698 days) in male patients and 66.5 days (range, 3-538 days) in female patients. An organ specialist was involved in all irAEs identified in male patients (100.0%, n=13/13) and in 57.1% (n=8/14) of irAEs occurring in female patients. Treatment with corticosteroids was initiated in 84.6% (n=11/13) and 71.4% (n=10/14) of irAEs occurring in male and female patients, respectively. Additional immunosuppressive drugs were more frequently applied in male than in female patients (38.5 vs. 7.1%).

IrAEs were resolved and ICIs were discontinued in 69.2% (n=9/13) of male patients and 71.4% (n=10/14) of female patients. In a similar proportion of male and female patients (15.4 vs. 14.3%), irAEs were resolved and ICIs were continued. In 14.3% of female patients (n=2/14) irAEs were resolved and ICIs were de-escalated from ipilimumab and nivolumab to nivolumab monotherapy, while 15.4% (n=2/13) of irAEs in male patients were ongoing at the cut-off date.

The median follow-up duration was 34.0 months. The overall response rate, including complete remission, partial remission and stable disease, was higher in male compared with female patients (74.1 vs. 58.3%). All patients had a higher median PFS in presence of irAEs than without irAEs (male patients, 19.9 vs. 4.4 months; log rank P=0.0089; female patients, 10.7 vs. 1.8 months; log rank P=0.43). Similarly, all patients had a higher median OS in the presence of irAEs (male patients, not estimable vs. 10.1 months; log rank P=0.02; female patients, 22.5 vs. 7.4 months; log rank P=0.24) (Fig. 1).

Discussion

In the cohort of patients with PAD treated with ICIs in the present study, a new onset of irAEs unrelated to the underlying PAD occurred in ~50% of the patients, with female patients being more frequently affected (58.3 vs. 48.1%). These data indicate a higher risk of irAEs in the presence of PAD compared with the cancer population treated in the clinic, where any grade of irAEs were reported in 38.4 and 28.1% of female and male patients, respectively (18). These results confirm female sex as a risk factor for experiencing irAEs (18,21).

By contrast, exacerbations of PAD were more common in male patients (38.5 vs. 14.3%), and this is likely related to differences in the type of PAD. In other cohorts (22,23), rheumatic disorders and inflammatory bowel disease were associated with a higher risk of exacerbation. Accordingly, in the present study, of the 7 patients with exacerbations, 3 had

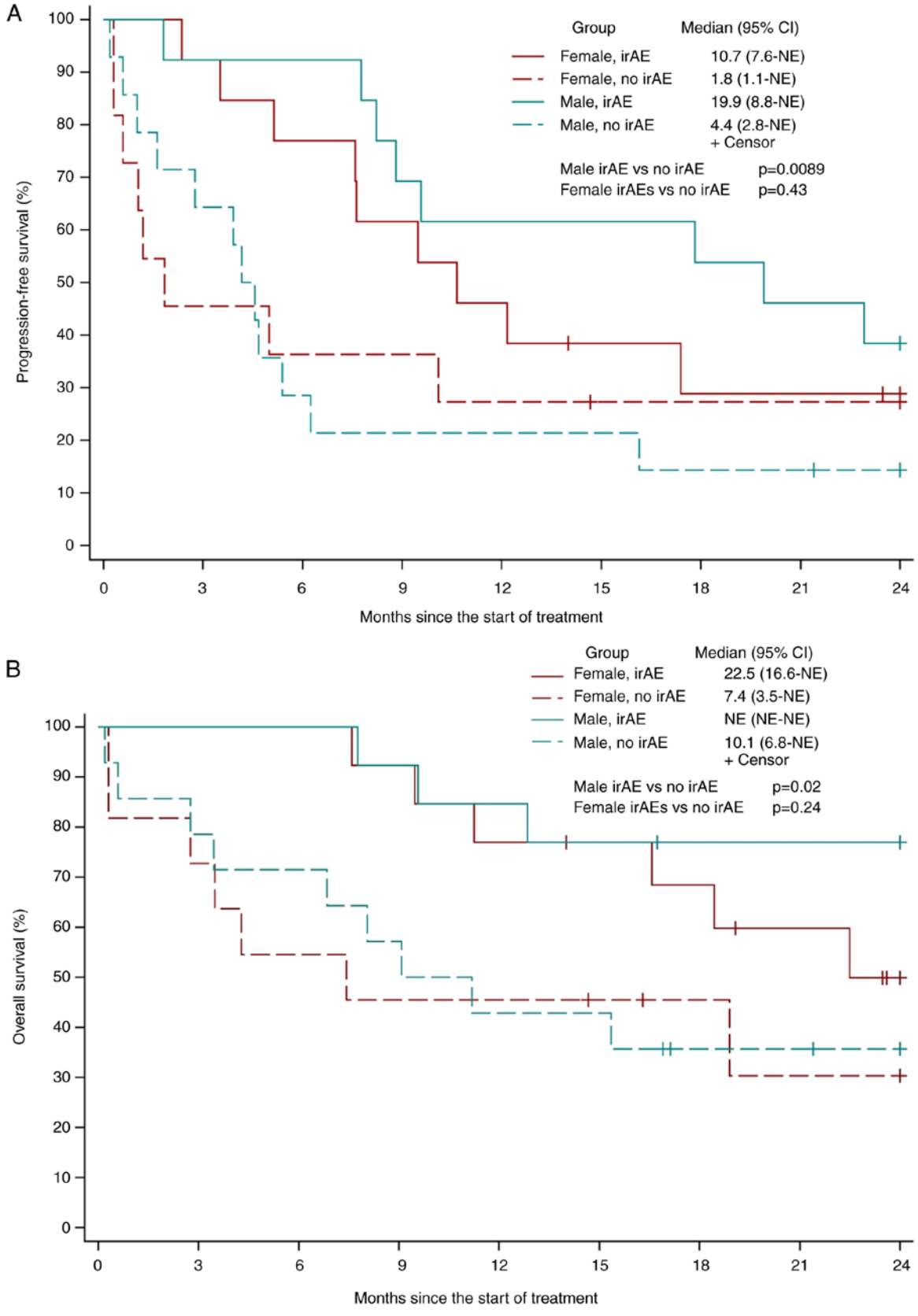

Figure 1. Progression-free survival and overall survival by sex. (A) A log-rank test was performed for progression-free survival for male patients with irAEs vs. no irAEs, (P=0.0089) and for female patients with irAEs vs. no irAEs (P=0.43). (B) A log-rank test was also performed for overall survival of male patients with irAEs vs. no irAEs (P=0.02) and for female patients with irAEs vs. no irAEs (P=0.24). CI, confidence interval; irAEs, immune-related adverse events; NE, not estimable.

arthritis and 2 had inflammatory bowel disease. Rheumatic disorders were the leading PAD in male patients, and ~50% of these patients showed an exacerbation, while endocrine disorders were more prominent in female patients. The total

rate of exacerbations in the cohort of the present study (n=7, 25.9%) is in the range of previous reports focusing on various cancer types such as melanoma, non-small cell lung cancer and urothelial carcinoma (range, 23-47%) (24,25). Previous studies showed exacerbation rates of 27-75% with anti-CTLA4 antibody (24,26), 16-38% with anti-PD1/PD-L1 antibody and 41-55% with a combination of these antibodies (15,23,26). In the cohort of the present study, patients with PAD were not less likely to receive combination ICI compared with patients with cancer without PAD receiving ipilimumab and nivolumab in 12-14% of cases (18).

The median time to irAE onset was shorter in patients with PAD compared with that in the cancer population treated at Bern University Hospital Cancer Center (69 vs. 85 days) (18). In addition, female patients with PAD more often had stage IV disease (83.3 vs. 66.7%) compared with the general population, which was possibly related to the higher proportion of lung cancer cases (54.2 vs. 37.5%) among the patients with cancer with PAD compared with the general population.

The majority of the irAEs were successfully managed with corticosteroids alone or in combination with additional immunosuppressive drugs. The prescription rate of additional immunosuppressive drugs in female patients with PAD (7.1%) was comparable to the general population (8.3%), and was higher in male patients with PAD (38.5%). The ranges of previously reported rates of new irAEs and ICI discontinuation among patients with cancer with PAD were 16-50 and 5-63%, respectively (26). In the cohort of the present study, a similar discontinuation rate of ~70% was observed. Based on these results, the outcome of patients with cancer and PAD receiving ICIs appears not to be inferior to that of the general population.

It is noteworthy that, as for the patients with cancer treated at Bern University Hospital Cancer Center (18), the occurrence of irAEs in patients with PAD was associated with a longer median OS time. In contrast to the general population, the survival benefit seems greater in male than in female patients with PAD, despite the higher frequency of immunosuppressive drug treatment in the male cohort (12). A recent meta-analysis has shown that the occurrence of irAEs is associated with improved response to ICIs (27), as irAEs are considered to be a bystander effect of T-cell activation (12). It is therefore conceivable that this effect outweighs the negative impact of corticosteroids on patient outcome. Also, the greater number of stage III cancer cases in the male cohort may have contributed as a confounding factor to the improved survival.

There is a requirement to involve organ specialists in the care of patients with active PAD before ICI initiation. IrAEs in patients with high levels of immunosuppression for PAD control may be difficult to manage. Furthermore, immunosuppression at the time of ICI initiation may compromise the efficacy of ICI treatments. In the cohort of the present study, a specialist was implicated in all irAEs cases in male patients, but only in 42.9% of the cases in female patients. This might be related to the fact that irAEs in male patients were more complex to manage. In male patients, irAEs were more likely to involve multiple sites, require additional immunosuppressive treatment and persist. A multidisciplinary evaluation of patients with PAD before ICI initiation could facilitate early detection of PAD exacerbation and management of irAEs, and improve outcome.

Given the higher incidence of ADs and irAEs in women (28), the investigation of potential sex differences in the safety and outcome of ICI in patients with PAD is critical. The analysis carried out as part of the current study, as well as other data, suggest that ICIs may be safely tolerated in patients with AD, but there are currently no prospective data to guide management. A phase 1b trial [AIM-NIVO, NCT03816345 (29)] is currently investigating nivolumab in 312 patients with cancer and PAD, and is expected to be completed by August 2023.

The present study has certain limitations. The observational and retrospective nature of the study, the small cohort size and the heterogeneity of the patient cohort may limit the robustness of conclusions and statistical analyses. In addition, the external validity may be restricted given that PAD was mostly in drug-free remission at ICI onset. However, the current study provides detailed observational real-world data segregated by sex, and contributes to the knowledge in this field.

Sex differences in irAEs with immune checkpoint inhibition and possible reasons have been previously described (30,31). Hormonal factors play a major role in the regulation of immune responses, as well as the expression of immune checkpoint proteins such as PD-1 (32,33). Other considerations include sex differences in the pharmacokinetics and pharmacodynamics of ICIs (34). Further research should assess the optimal dosage and dosing regimen for ICIs in male and female patients given that sex, body weight, body surface area and serum albumin appear to affect clearance of ICIs (34,35). As published data on the interplay between ICI treatments, PAD and sex are scant, the analyses presented in the current study are an initial real-world description that could guide the next steps to evaluate clinical relevance. The higher proportion of female patients with PAD experiencing irAEs when treated with ICIs should be confirmed in a larger patient series. Additionally, the small cohort of the present study indicated that the occurrence of irAEs may impact PFS and OS times among both male and female patients; however, it lacked the statistical power to assess any differential association between sexes. This should be assessed in a larger study.

In conclusion, the results of the current study show that, although female patients are more prone to experiencing irAEs, exacerbation of PAD is more common in male patients. Male patients with PAD flare require more corticosteroids and additional immunosuppressive treatment, possibly related to the higher frequency of rheumatic and gastrointestinal PAD. These findings highlight the need for a better understanding of sex-related factors influencing the outcome of AD and irAEs.

Acknowledgements

The authors would like to thank Dr Muriel N. Wahli (Department of Medical Oncology, Inselspital Bern, Bern University Hospital, University of Bern, Bern, Switzerland) for providing assistance with data collection.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ML collected and analyzed the data. ML and AR performed the statistical analyses. ML and BCÖ confirm the authenticity of all the raw data. LC analyzed and interpreted data, and wrote the manuscript, and BCÖ designed the study and wrote the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Ethics Commission of the Canton of Bern (approval no. 2021-01335).

Patient consent for publication

Not applicable.

Competing interests

ML and AR declare that they have no competing interests. LC reports research/non-financial support, advisory fee and stock ownership from Gilead Sciences, F. Hoffmann-La Roche, Novartis, Pfizer, Bristol-Myers Squibb and Sanofi. BCÖ declares receiving institutional honoraria for lectures and advisory boards from BMS, MSD, Merck, Ipsen, Roche, Pfizer, Novartis, Janssen and Sanofi.

References

1. van der Kooij MK, Suijkerbuijk KPM, Aarts MJB, van den Berkmortel FWPJ, Blank CU, Boers-Sonderen MJ, van Breeschoten J, van den Eertwegh AJM, de Groot JWB, Haanen JBAG, *et al*: Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease: A cohort study. Ann Intern Med 174: 641-648, 2021.
2. Cortellini A, Buti S, Santini D, Perrone F, Giusti R, Tiseo M, Bersanelli M, Michiara M, Grassadonia A, Brocco D, *et al*: Clinical outcomes of patients with advanced cancer and pre-existing autoimmune diseases treated with anti-programmed death-1 immunotherapy: A real-world transverse study. Oncologist 24: e327-e337, 2019.
3. Beaver JA and Pazdur R: The wild west of checkpoint inhibitor development. N Engl J Med 386: 1297-1301, 2022.
4. Granier C, De Guillebon E, Blanc C, Roussel H, Badoual C, Colin E, Saldmann A, Gey A, Oudard S and Tartour E: Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. ESMO Open 2: e000213, 2017.
5. Cancer Institute N: Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 2017.
6. Naidoo J, Murphy C, Atkins MB, Brahmer JR, Champiat S, Feltquate D, Krug LM, Moslehi J, Pietanza MC, Riemer J, *et al*: Society for immunotherapy of cancer (SITC) consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events (irAEs) terminology. J Immunother Cancer 11: e006398, 2023.
7. Tarhini AA, Lee SJ, Hodi FS, Rao UNM, Cohen GI, Hamid O, Hutchins LF, Sosman JA, Kluger HM, Eroglu Z, *et al*: Phase III study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon Alfa-2b for resected high-risk melanoma: North American Intergroup E1609. J Clin Oncol 38: 567-575, 2020.
8. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, *et al*: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 377: 1345-1356, 2017.
9. Eggermont AMM, Blank CU, Mandalà M, Long GV, Atkinson VG, Dalle S, Haydon AM, Meshcheryakov A, Khattak A, Carlino MS, *et al*: Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): Distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 22: 643-654, 2021.
10. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, Sznol M, Long GV, Li H, Waxman IM, *et al*: Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. J Clin Oncol 35: 785-792, 2017.
11. Johnson DB, Nebhan CA, Moslehi JJ and Balko JM: Immune-checkpoint inhibitors: Long-term implications of toxicity. Nat Rev Clin Oncol 19: 254-267, 2022.
12. Das S and Johnson DB: Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 7: 306, 2019.
13. Postow MA, Sidlow R and Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378: 158-168, 2018.
14. Mangan BL, McAlister RK, Balko JM, Johnson DB, Moslehi JJ, Gibson A and Phillips EJ: Evolving insights into the mechanisms of toxicity associated with immune checkpoint inhibitor therapy. Br J Clin Pharmacol 86: 1778-1789, 2020.
15. Pantuck M, McDermott D and Drakaki A: To treat or not to treat: Patient exclusion in immune oncology clinical trials due to preexisting autoimmune disease. Cancer 125: 3506-3513, 2019.
16. Khan SA, Pruitt SL, Xuan L and Gerber DE: Prevalence of autoimmune disease among patients with lung cancer: Implications for immunotherapy treatment options. JAMA Oncol 2: 1507-1508, 2016.
17. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F and Shoenfeld Y: Sex-based differences in autoimmune diseases. Ann Ist Super Sanita 52: 205-212, 2016.
18. Wahli MN, Hayoz S, Hoch D, Ryser CO, Hoffmann M, Scherz A, Schwacha-Eipper B, Häfliger S, Wampfler J, Berger MD, *et al*: The role of immune checkpoint inhibitors in clinical practice: An analysis of the treatment patterns, survival and toxicity rates by sex. J Cancer Res Clin Oncol: Aug 23, 2022 (Epub ahead of print).
19. Amin M, Edge S and Greene F: AJCC cancer staging manual. 8th edition. Springer, 2017.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
21. Duma N, Abdel-Ghani A, Yadav S, Hoversten KP, Reed CT, Sitek AN, Enninga EAL, Paludo J, Aguilera JV, Leventakos K, *et al*: Sex differences in tolerability to anti-programmed cell death protein 1 therapy in patients with metastatic melanoma and non-small cell lung cancer: Are we all equal? Oncologist 24: e1148-e1155, 2019.
22. Alexander S, Swami U, Kaur A, Gao Y, Fatima M, Ginn MM, Stein JE, Grivas P, Zakharia Y and Singh N: Safety of immune checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease. Ann Transl Med 9: 1033, 2021.
23. Boland P, Pavlick AC, Weber J and Sandigursky S: Immunotherapy to treat malignancy in patients with pre-existing autoimmunity. J Immunother Cancer 8: e000356, 2020.
24. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, Guminski A, Puzanov I, Lawrence DP, Buchbinder EI, *et al*: Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2: 234-240, 2016.
25. Tison A, Quéré G, Misery L, Funck-Brentano E, Danlos FX, Routier E, Robert C, Loriot Y, Lambotte O, Bonniaud B, *et al*: Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: A nationwide, multicenter cohort study. Arthritis Rheumatol 71: 2100-2111, 2019.
26. Tang H, Zhou J and Bai C: The efficacy and safety of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease. Front Oncol 11: 625872, 2021.

27. Fan Y, Xie W, Huang H, Wang Y, Li G, Geng Y, Hao Y and Zhang Z: Association of immune related adverse events with efficacy of immune checkpoint inhibitors and overall survival in cancers: A systemic review and meta-analysis. Front Oncol 11: 633032, 2021.
28. Unger JM, Vaidya R, Albain KS, LeBlanc M, Minasian LM, Gotay CC, Henry NL, Fisch MJ, Lee SM, Blanke CD and Hershman DL: Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. J Clin Oncol 40: 1474-1486, 2022.
29. Ileana Dumbrava EE, Suarez-Almazor ME, Painter J, Johanns T, Dougan ML, Cappelli L, Bingham CO, Wang Y, Gupta S, Warner BM, *et al*: A phase Ib study of nivolumab in patients with autoimmune disorders and advanced malignancies (AIM-NIVO). J Clin Oncol 38 (Suppl): TPS3158, 2020.
30. Özdemir BC, Coukos G and Wagner AD: Immune-related adverse events of immune checkpoint inhibitors and the impact of sex-what we know and what we need to learn. Ann Oncol 29: 1067, 2018.
31. Triggianese P, Novelli L, Galdiero MR, Chimenti MS, Conigliaro P, Perricone R, Perricone C and Gerli R: Immune checkpoint inhibitors-induced autoimmunity: The impact of gender. Autoimmun Rev 19: 102590, 2020.
32. Polanczyk MJ, Hopke C, Vandenbark AA and Offner H: Estrogen-mediated immunomodulation involves reduced activation of effector T cells, potentiation of Treg cells, and enhanced expression of the PD-1 costimulatory pathway. J Neurosci Res 84: 370-378, 2006.
33. Ozdemir BC and Dotto GP: Sex hormones and anticancer immunity. Clin Cancer Res 25: 4603-4610, 2019.
34. Centanni M, Moes DJAR, Trocóniz IF, Ciccolini J and van Hasselt JGC: Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet 58: 835-857, 2019.
35. Hurkmans DP, Sassen SDT, de Joode K, Putter L, Basak EA, Wijkhuijs AJM, Joerger M, Debets R, Koch BCP, Van der Leest CH, *et al*: Prospective real-world study on the pharmacokinetics of pembrolizumab in patients with solid tumors. J Immunother Cancer 9: e002344, 2021.