Auto immune disease -->IO

Dr M V Chandrakanth

Narayana Hospital,Kolkata

OXFORD

JNCI J Natl Cancer Inst (2022) 114(8): djac046

https://doi.org/10.1093/jnci/djac046
First published online February 21, 2022
Brief Communications

Pre-Existing Autoimmune Disease and Mortality in Patients Treated with Anti-PD-1 and Anti-PD-L1 Therapy

Kimberly Tang, BA [1], Bruce C. Tiu, BS,[1,2] Guihong Wan, PhD,[1,3] Shijia Zhang, BA,[1,3] Nga Nguyen, BA,[1] Bonnie Leung, BSc,[1] Alexander Gusev, PhD,[4] Kerry L. Reynolds, MD,[5] Shawn G. Kwatra, MD,[6,‡] Yevgeniy R. Semenov, MD, MA [1,2,*,‡]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA; [2]Department of Dermatology, Harvard Medical School, Boston, MA, USA; [3]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA; [4]Department of Medicine, Dana Farber Cancer Institute, Boston, MA, USA; [5]Department of Medicine, Division of Oncology, Massachusetts General Hospital, Boston, MA, USA; and [6]Department of Dermatology, Johns Hopkins University, Baltimore, MD, USA

Introduction

- ICIs are approved for treatment of > 19 malignancy types
- ICIs cause life threatening irAEs that resemble ADs
- Clinical Trials leading to ICI approval **excluded** patients with AD because of:
    1. Concerns of exacerbating their underlying AD
    2. Increasing risk of treatment-induced irAEs
    3. Achieving a poorer ICI response
- This study investigates
    - ***"Impact of Baseline History of AD on Survival among Cancer Patients"***

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Methods

- Retrospective Analysis of Observational data from TriNetX Diamond network (EHR of 200 million patients)
- Log-rank test was used to calculate P values, and a 2-sided P value less than 0.05 was considered statistically significant for exploratory analyses.
- Hazard ratios were calculated, and a Benjamini-Hochberg (BH) correction was used to adjust for multiple comparisons.
- **ICI included in analysis:**
    1. Anti – PD – 1: cemiplimab, nivolumab, or pembrolizumab
    2. Anti – PD –L1: atezolizumab, avelumab, or durvalumab
- **4 most common malignancies for ICIs analysed**
    - (*International Classification of Diseases* 10th edition) :
    1. C34: bronchus and lung
    2. C15-26: digestive organs
    3. C43: melanoma
    4. C64-68: urinary tract

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Propensity score-matched Baseline Characteristics for Patients Treated with anti-PD-1 or anti-PD-L1 therapy

Baseline characteristic	ICI with baseline autoimmunity	ICI without baseline autoimmunity	P[a]
Total No. of patients	17 497	17 497	
No. alive	10 668	10 827	
No. deceased	6829	6670	
Mean age at index (SD), y	68.6 (10.9)	68.9 (10.6)	.001
Sex, No. (%)			
Male	8923 (51.0)	8875 (50.7)	.61
Female	8564 (48.9)	8617 (49.2)	.57
Unknown	10 (0.1)	10 (0.1)	.99
Race and ethnicity, mean No. (%)[b]			
Asian non-Hispanic	52 (0.3)	50 (0.3)	.84
Black non-Hispanic	542 (2.4)	475 (2.1)	.03
Hispanic or Latino	428 (2.4)	370 (2.1)	.04
White non-Hispanic	4854 (27.7)	4826 (27.6)	.74
Cancer type, mean No. (%)			
Digestive organs	3378 (19.3)	3402 (19.4)	.75
Bronchus and lung	11 079 (63.3)	11 118 (63.5)	.67
Melanoma of skin	3948 (22.6)	3903 (22.3)	.56
Urinary tract	3307 (18.9)	3235 (18.5)	.32
Ill-defined, other secondary, and unspecified sites[c]	13 524 (77.3)	13 617 (77.8)	.23

- [a]P values were included to demonstrate that the matching algorithm has worked. Baseline characteristics were compared using v2 tests for categorical variables and independent- sample t tests for continuous variables, 2 sided. [b]Demographic data was not available for all patients in TriNetX. Propensity score matching was used to match patients with known demographics. Patients with unknown demographics (67.2%) were matched based on unknown status. [c]Based on International Classification of Diseases code for secondary malignancy to identify patients with distant metastases of their underlying cancer.

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Results

- **For the primary analysis:**
  - 17,497 patients who had pre-existing AD Vs. 17,497 matched non – AD patients.
- **Median duration of follow-up:**
  - Study Population: 1.76 years
  - Control Populations: 1.84 years

Overall, patients with history of AD were ***NOT*** at statistically significantly higher risk of mortality than non-AD patients (HR = 1.03, 95% CI = 1.00 to 1.07; P=.05)

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Association between baseline autoimmunity and survival among patients treated with Anti – PD – 1 or Anti – PD – L1 Therapy

Autoimmune diagnosis	No.	Hazard ratio (95% CI)[a]	P[b]
Myasthenia gravis	108	1.31 (0.85 to 2.02)	.21
Morphea	205	1.29 (0.93 to 1.79)	.13
Vasculitis	494	1.18 (0.97 to 1.44)	.09
Scleroderma	128	1.12 (0.77 to 1.63)	.55
Type 1 diabetes	3960	1.11 (1.03 to 1.19)	.002
Psoriasis	1827	1.07 (0.96 to 1.19)	.24
Mucositis	3181	1.04 (0.97 to 1.12)	.30
Inflammatory bowel disease	10 415	1.03 (0.99 to 1.08)	.17
Ankylosing spondylitis	164	1.02 (0.72 to 1.46)	.90
Rheumatoid arthritis	3176	1.01 (0.93 to 1.09)	.80
Autoimmune hepatitis	109	1.00 (0.64 to 1.57)	.99
Graves disease	416	0.96 (0.76 to 1.20)	.68
Multiple sclerosis	281	0.93 (0.70 to 1.23)	.60
Dermatomyositis	79	0.93 (0.55 to 1.55)	.77
Atopic dermatitis	1057	0.89 (0.77 to 1.03)	.12
Systemic lupus erythematosus	541	0.89 (0.74 to 1.06)	.19
Addison disease	920	0.88 (0.76 to 1.01)	.08
Bullous pemphigoid	59	0.86 (0.46 to 1.60)	.64
Hashimoto disease	655	0.75 (0.62 to 0.90)	.002
Celiac disease	241	0.74 (0.57 to 0.97)	.03
Lichen planus	292	0.70 (0.53 to 0.93)	.01
Alopecia areata	94	0.61 (0.39 to 0.97)	.04
Vitiligo	161	0.52 (0.34 to 0.81)	.003
Any cutaneous diagnosis	17 497	1.03 (1.00 to 1.07)	.05

- History of **Hashimoto disease** and **vitiligo** was statistically significantly protective of mortality after BH correction
- History of **celiac disease**, **lichen planus**, and **alopecia areata** was associated with a protective effect *but did not meet the BH threshold for statistical significance*
- *Conversely*, patients with **type 1 diabetes** had statistically significant but modest increase in mortality compared with patients without AD history

[a]Hazard ratio of the impact of pre-existing autoimmune disease on overall survival when compared with patients without pre-existing autoimmune disease

[b]Benjamini-Hochberg (BH) P value of statistical significance at .006. Log-rank test was used to calculate P values, 2-sided.

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Results

- **Duration of ICI therapy was similar between AD patients and non-AD patients (7.2 vs 7.5 cycles of ICI)**
  - ✓ **Suggesting that history of AD did not lead to a clinically significant increase in ICI discontinuation.**
- **No increased risk of mortality with:**
  - ✓ **Anti – PD – L1 monotherapy (HR = 1.08, 95% CI = 0.98 to 1.18; P = .13)**
  - ✓ **Combination PD – 1 and CTLA – 4 inhibition (HR = 1.04, 95% CI = 0.92 to 1.18; P = .54)**
- **Mildly increased risk of mortality with:**
  - ✓ **Anti – PD – 1 monotherapy (HR = 1.14, 95% CI = 1.10 to 1.18; P<.001),**
    - ❖ This was largely driven by history of **rheumatoid arthritis**, **inflammatory bowel disease**, **type 1 diabetes**, and **mucositis**.

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Final Hypothesis

- Use of Systemic Steroids for AD may have differential effect on mortality
- Hashimoto disease, vitiligo, lichen planus, celiac disease, and alopecia areata were seen here to be protective against mortality and are also diseases not commonly treated with systemic corticosteroids
- On the contrary, rheumatoid arthritis, inflammatory bowel disease, and mucositis are diseases that tend to be more severe, often requiring systemic immunosuppression, which may be responsible for the increased association with mortality in subgroup analyses
- Limitations of TriNetX prevented reliable analysis on the use and impact of corticosteroids on mortality in the setting of AD prior to and during ICI therapy, which should be the subject of future studies

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Hypothesis: Use of Systemic Steroids for AD May Have Differential Effect on Mortality

Protective Against Mortality:
Hashimoto disease, vitiligo, lichen planus, celiac disease, and alopecia areata

↓

These Diseases Are Also Diseases Not Commonly Treated with Systemic Corticosteroids

Increased Risk of Mortality:
Rheumatoid arthritis, inflammatory bowel disease, and mucositis (More Severe Diseases)

↓

These Diseases Often Require Systemic Immunosuppression

! Limitations of TriNetX prevented reliable analysis on the use and impact of corticosteroids on mortality in the setting of AD prior to and during ICI therapy, which should be the subject of future studies

ICI: Immune Checkpoint Inhibitor; irAEs: immune-related adverse events; AD: Autoimmune Disorders

Thank You