Risk of Latent Tuberculosis Reactivation in Patients Treated with Checkpoint Inhibitors Immunotherapy Compared to Other Anti-Cancer Therapies including Hematopoietic Cell Transplantation

Alexandre E. Malek, MD[1], Patrick Chaftari, MD[2], Hiba R. Dagher, MD[1], Ray Hachem, MD[1], Anne Marie Chaftari, MD[1], George M. Viola, MD[1], Issam I. Raad, MD[1]
[1]Department of Infectious Diseases, Infection Control and Employee Health; [2]Department of Emergency Medicine; The University of Texas MD Anderson Cancer Center, Houston, Texas

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Correspondence: Alexandre E. Malek, MD
E-mail: Alex.e.malek@gmail.com

BACKGROUND

- Checkpoint inhibitor (CPI) immunotherapy has ushered cancer treatment into a potentially curative era.
- The risk of latent tuberculosis infection (LTBI) reactivation in cancer patients receiving CPI remains largely unknown.
- We assessed LTBI therapy and outcomes between cancer patient receiving CPI versus conventional chemotherapy (CC) and hematopoietic cell transplantation (HCT) recipients.

METHODS

- We performed a comparative single-center retrospective cohort study of adult patients with LTBI (positive T-SPOT TB test) between April 2016 and May 2020, who received treatment with CPI versus those who received other anti-cancer therapies including CC alone or HCT.
- The primary objective was to assess the risk of LTBI reactivation and evaluate the adverse events of LTBI therapy between the three groups.
- We evaluated patients' characteristics, treatment modality, immune related adverse events (irAEs), and outcomes.
- Tuberculosis reactivation was defined by clinical signs and symptoms, microbiologic documentation, and/or PCR or histopathological examination.
- Chi-square or Fisher's exact test were used for categorical variables.

RESULTS

- A total of 104 patients with LTBI were identified and were analyzed into three distinct groups (**Table 1**): CPI (32 patients, 31%), CC alone (35 patients, 34%), and HCT [37 patients, 35% (7 autologous versus 30 allogeneic)].
- The majority of patients in the CPI group (97%) had solid tumors compared to 51% in the CC group.
- Nivolumab was the most commonly used CPI agent in 13 patients (44%), followed by pembrolizumab, 10 Pts (31%), (**Table 2**).

RESULTS

Table 1. LTBI analysis among cancer patients with CPI, CC and HCT

Characteristics	HCT (n=37) N (%)	CC (n=35) N (%)	CPI (n=32) N (%)	p-value	Pairwise comparisons with significant differences *
Age (years), median (IQR)	58 (48-66)	64 (54-70)	65 (60-72)	0.039	HCT vs CPI: p=0.012
Sex, male	29 (78)	18 (51)	22 (69)	0.051	
Race				0.16	
White	20 (54)	10 (29)	15 (47)		
Black	5 (14)	2 (6)	5 (16)		
Hispanic	1 (3)	1 (3)	0 (0)		
Asian	3 (8)	10 (26)	5 (16)		
Others	8 (22)	13 (37)	7 (22)		
Type of cancer				< .0001	HCT vs CC: p< .0001
Hematologic malignancy	36 (97)	17 (49)	1 (3)		HCT vs CPI: p< .0001
Solid tumor	1 (3)	18 (51)	31 (97)		CC vs CPI: p< .0001
Type of HCT					
Allo	30 (81)				
Auto	7 (19)				
HIV	1 (3)	0 (0)	0 (0)	> .99	
COPD	5 (14)	4 (11)	8 (25)	0.27	
DM	16 (43)	7 (20)	10 (31)	0.11	
CKD	18 (49)	8 (23)	9 (28)	0.05	None
Smoker	12 (32)	19 (54)	11 (34)	0.12	
HTN	30 (81)	19 (54)	20 (63)	0.048	HCT vs CC: p=0.015
INH treatment	18 (49)	14 (40)	21 (66)	0.10	
INH toxicity	0/18 (0)	1/14 (7)	4/21 (19)	0.16	
TB reactivation	0 (0)	2 (6)	0 (0)	0.20	
Mortality	9 (24)	5 (14)	10 (31)	0.25	
Days of f-up,median (IQR)[a]	449 (149-773)	564 (198-1058)	364 (155-571)	0.21	

*The α levels were adjusted using Holm's sequential Bonferroni adjustment to control type I error.
[a]The follow up ended either on May 1, 2020 or date of death for those who died.

Table 2. CPI treatment and irAEs of CPI patients

Characteristics	CPI (n=32) N (%)
CPI agents	
Nivolumab	13 (44)
Pembrolizumab	10 (31)
Atezolizumab	5 (16)
Ipilimumab	4 (13)
irAEs	11 (34)
irAEs required corticosteroids	9/11 (82)

Abbreviation:
Allo: allogeneic; Auto: autologous; CC: conventional chemotherapy; CPI: checkpoint inhibitor; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; f-up: follow up; HCT: hematopoietic cell transplantation; HTN: hypertension; HIV: human immunodeficiency virus; IQR: interquartile; INH: isoniazid; irAEs: immune-related adverse events. N/A: not applicable.

RESULTS

- Confirmed TB reactivation infections were identified in only 2 patients in the CC group (6%; p=0.20). None of these 2 patients had received LTBI therapy or corticosteroids prior to the diagnosis.
- In the CPI group, 21 pts (66%) received Isoniazid (INH) therapy for LTBI, versus 18 patients (49%) in the HCT group and 14 patients (40%) in the CC group (p=0.10).
- Immune-related adverse events (IrAEs) were reported in 11 pts (34%) patients, and 9 (82%) of them received corticosteroids. Out of 21 of CPI patients whom received INH, 4 (19%) developed possible INH-induced liver toxicities leading to interruption of medication versus 1 (7%) patient which had hepatitis in CC group versus none of HCT patients (p=0.16).
- Our data suggest that latent tuberculosis reactivation remains rare in the 3 groups.
- Hepatotoxicity is relatively common in patients treated with CPI and INH.

CONCLUSIONS

- **Cancer patients with LTBI treated with checkpoint inhibitor and Isoniazid, have increased risk of hepatotoxicity compared to those receiving INH with other anti-cancer therapies.**
- **Caution and close monitoring are required to avoid significant hepatic injury and interruption of LTBI and lifesaving oncological therapies.**