Predictive Factors of Thyroid Adverse Events in Neoadjuvant Immunotherapy for Triple-Negative Breast Cancer

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Abstract

Thyroid dysfunction is among the most common immune-related adverse events (irAEs) of immune checkpoint inhibitors (ICIs). This study aimed to investigate the prevalence, risk factors, potential pathogenesis and prognostic implications of thyroid irAEs in triple-negative breast cancer (TNBC) patients receiving neoadjuvant anti-PD-1 therapy combined with chemotherapy, based on data from the TREND trial.

Multivariate analysis identified baseline thyroglobulin antibody (TgAb) (OR 10.483, p=0.005) as significantly associated with increased risk of thyroid irAEs. Importantly, we observed strikingly divergent trajectories in peripheral immune cell changes between patients who developed thyroid irAEs and those who did not. The findings implicate early CD4+T cell elevation in pathogenesis and suggest that the occurrence of irAEs may be an indicator of favorable early treatment response. These may assist clinicians in identifying patients at elevated risk for irAEs during ICI therapy, thereby improving patient management in clinical practice.

Introduction

In recent years, ICIs have indeed revolutionized cancer treatment[1]. With the promising outcomes of clinical trials such as KEYNOTE-522[2] and IMpassion031[3], the integration of neoadjuvant ICIs with chemotherapy has emerged as a novel trend in the treatment of TNBC without distant metastasis.

While achieving therapeutic effects, immunotherapy was applicated more cautiously in early TNBC receiving neoadjuvant therapy due to the occurrence of severe adverse reactions. Among them, landmark trials including ISPY-2[4] and GeparNuevo[5] identified thyroid dysfunction as the most common irAEs. Multiple studies have indicated that the baseline TgAb positivity may be linked to an increased risk of developing thyroid-related irAEs during ICI therapy[6]. However, these findings are largely confined to adjuvant immunotherapy in cancers with high intrinsic immunogenicity such as melanoma and non-small cell lung cancer. Critically, no studies to date have investigated the risk factors or prognostic significance of thyroid irAEs during neoadjuvant immunotherapy for TNBC.

We recently conducted a phase II prospective clinical trial called TREND, in which patients received tislelizumab every three weeks for eight cycles plus nab-paclitaxel weekly for four cycles, followed by four cycles of epirubicin-cyclophosphamide every three weeks prior to surgery[7]. In this study, we aimed to assess the prevalence and clinical relevance of thyroid irAEs. We further evaluated potential risk factors associated with the onset of thyroid irAEs and their correlation with clinical outcomes.

Methods and Materials

The TREND study was a single-arm, single-center trial involving TNBC patients treated with tislelizumab combined with nab-paclitaxel, followed by epirubicin-cyclophosphamide before surgery. Data on demographics, thyroid function, anti-thyroid autoantibodies were collected for univariate and multivariate logistic regression models to identify risk factors. Peripheral immune analysis and whole-exome sequencing (WES) was performed to identify underlying mechanisms associated with thyroid irAEs.

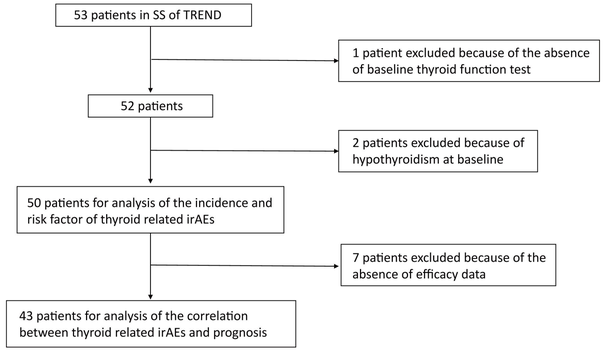


Figure 1. Patient selection and exclusion criteria.

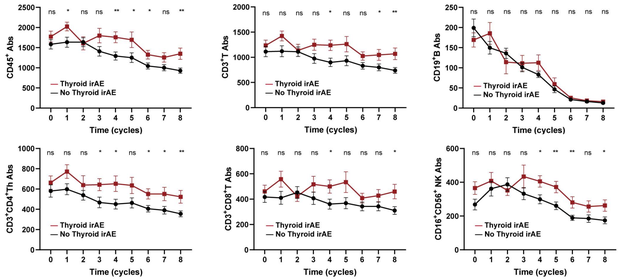


Figure 2. Differential dynamic changes in lymphocyte subsets (CD45+ Abs, CD3+T Abs, CD19+B Abs, CD4+Th Abs, CD8+T Abs, CD16+CD56+ NK Abs) between patients with and without thyroid irAEs.

Results

- Among 50 analyzed patients, 14 (28%) developed thyroid irAEs.
- Multivariate analysis identified baseline TgAb (OR 10.483, p=0.005) as significantly associated with increased risk of thyroid irAEs.
- Compared to unaffected patients, those developing thyroid irAEs exhibited substantially greater TgAb elevation and more pronounced thyroid peroxidase antibody (TPOAb) fluctuations.
- Importantly, we observed strikingly divergent trajectories in peripheral immune cell changes between patients who developed Thyroid irAEs and those who did not.
- Paired analysis of baseline and cycle one peripheral immune indices showed a transient increase in CD3+ T cells and CD4+ Th cells frequencies as early as after the first treatment cycle in the irAEs group.

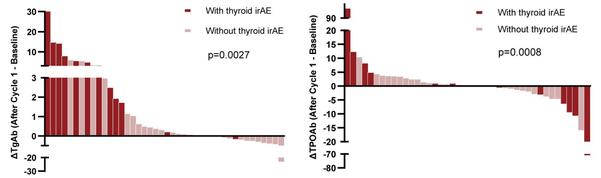


Figure 3. Change in TgAb and TPOAb levels after one treatment cycle.

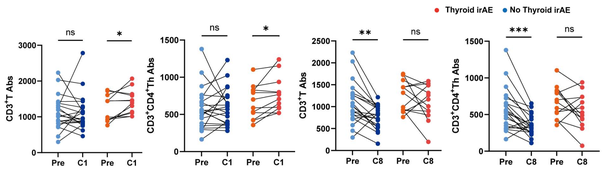


Figure 4. Dotplots of paired analysis of lymphocyte subsets (CD3+T Abs, CD4+Th Abs) before and after one/eight cycles of neoadjuvant treatment.

- We observed comparable TMB between patients with or without thyroid irAEs. We further found that all the three patients who experienced thyroid irAEs harbored KLF17 and LRIG1 mutations in their tumors.
- Potential link were found between thyroid irAEs and early response, wherein heightened systemic immune activation concurrently accelerates anti- tumor efficacy.

Discussion

The frequency of irAEs varies across different ICI treatments. Colitis is most common in patients receiving anti-CTLA-4 therapy, whereas thyroid irAEs are more frequent during anti-PD-1 treatment. Women are already at a higher risk for thyroid disorders and are more likely than men to develop hypothyroidism following ICI therapy. Therefore, the combination of neoadjuvant anti-PD-1 therapy and chemotherapy in TNBC makes the TREND trial ideal for investigating the underlying mechanism of thyroid irAEs in early-stage patients. Key findings include distinct dynamic changes in thyroid-related antibodies and peripheral blood profiles between patients who developed thyroid irAEs and those who did not. Importantly, patients experiencing thyroid irAEs demonsrated a higher likelihood of achieving early treatment response. These findings collectively suggest that the patient's global immune status plays a critical role in both the development of irAEs and the enhanced therapeutic efficacy.

The main limitations of our study are the relatively small sample size and the infeasibility of performing WES analysis on more patients due to limited tissue availability during surgery. Future big-scale phase III trials are awaited to expand the patient cohort and validate our findings. Additionally, our survival data are currently immature, we will continue to monitor patients and report updated analyses once sufficient follow-up is achieved.

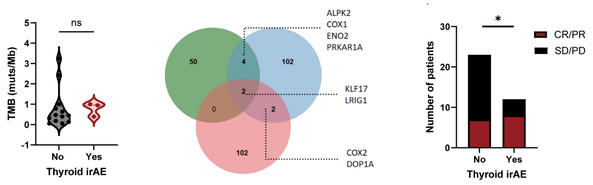


Figure 5. WES and the incidence of thyroid irAEs and early treatment response profiles.

Conclusions

This study represents the first investigation into predictive factors for thyroid irAEs and their association with treatment outcomes in TNBC patients receiving neoadjuvant immunotherapy based on TREND, a phase II prospective clinical trial. This work provides mechanistic insights into pathogenesis of irAEs and may inform clinical strategies for optimizing immunotherapy management.

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