LETTER to the EDITOR

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The Silent Threat of Interplay between Immune Checkpoint Inhibitors and Herbal Medicines

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Dear Editor

The recent publication of 'Immune-Related Adverse Events due to Concomitant Use of Immune Checkpoint Inhibitors and Chinese Herbal Medicines: A Study Based on a Japanese Adverse Event Database' has piqued my interest. Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, offering new hope for patients [1–3]. However, the interplay between programmed death ligand-1 (PDL-1)-expressing tumor cells and PD1, the most common checkpoint receptor-ligand complex, has been shown to dampen anti-tumor responses, thereby facilitating tumor growth. Conversely, the blockade of this immunosuppressive interaction has been demonstrated to rescue NK cell activity, validated in various human cancer settings [4].

The study in question examines the concomitant use of ICIs and traditional Chinese herbal medicines, specifically Hozai, which consists of three sub-formulas: Ninjinyoeito (NYT), Hochuekkito (HET), and Juzentaihoto (JTT) [5, 6]. The administration of JTT was shown to change NKp46 expression and CD314 in specific CD16-CD56 and CD16+CD56 cell fractions [4]. NKp46 is expressed by all human NK cells. The surface density of NKp46 varies among NK cells, and there is a precise correlation between the NKp46 phenotype of NK clones and their natural cytotoxicity against HLA-class I-unprotected cells. The NKp46 phenotype of NK clones is correlated with their ability to lyse HLA-class I-unprotected autologous cells. Moreover, NKp46 plays a crucial role in the natural cytotoxicity mediated by freshly derived NK cells [7]. The NKp46 expression in the CD16-CD56bright fraction increased significantly in a time dependent manner. In contrast, the CD16+CD56dim fraction exhibited a decrease in NKp46 expression. Similarly, CD314, a C-type lectin-like receptor, designated as NK group 2D (NKG2D) expression showed a significant increase in the CD16-CD56high fraction. While only CD16+CD56dim fraction displayed a significant increase in CD314 expression, both NK cell fractions showed a significant increase on CD161 expression—which mark pro-inflammatory NK cell subset [8]. These changes suggest that JTT administration induces distinct temporal patterns of activation in NK cell markers, with implications for immune function and disease modulation [9].

These formulas have been reported to alleviate cancer-associated fatigue [5, 6]. This study's pioneering endeavor to investigate the correlation between immune-related adverse events (irAEs) and concomitant use of ICIs and Hozai is substantiated by the absence of prior reports. Therefore, this is of significant contribution to the field.

The study's findings suggest that the long-term use of herbal medicines, which are often perceived as harmless [10, 11], may actually be detrimental and potentially exacerbate clinical conditions in patients treated with ICIs. The concomitant administration of herbal supplements with prescription drugs poses a significant risk of herb-drug interactions, particularly when considering medications with a narrow therapeutic index [12].

The cytochrome P3A4 (CYP3A4) enzyme plays a pivotal role in the metabolism of over 80% of prescription drugs and herbal supplements, rendering it a critical factor in determining herb-drug interactions [13]. The chemical properties of interacting drugs include being a CYP enzyme substrate, P glycoprotein (P-gp) transporter substrate, or CYP inducer/inhibitor. The challenge lies in overcoming competition between CYPs and P-gp, which are key contributors to drug metabolism and excretion [14].

Clinical trials often focus on the efficacy of herbal supplements and exclude patients taking prescribed medications, thereby obscuring the potential for herb-drug interactions [15]. As such, there is a pressing need for studies that investigate the interactions between herbal supplements and prescription drugs. The identification of herb-drug interactions can have significant implications for patient safety, particularly in the context of medications that require close monitoring of blood drug levels [12].

Acknowledgments

None.

Conflict of Interest

There is no conflict of interest to declare.

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Reply to the Letter to the editor: The Silent Threat of Interplay between Immune Checkpoint Inhibitors and Herbal Medicines Dear Editor

Dear Editor:

Thank you very much for notifying me about the Letter to the Editor regarding my manuscript, 'Immune-Related Adverse Events due to Concomitant Use of Immune Checkpoint Inhibitors and Chinese Herbal Medicines: A Study Based on a Japanese Adverse Event Database'. I sincerely appreciate the opportunity to delve deeper into the subject, having taken the points raised in the letter to heart.

I was particularly intrigued by the detailed analysis of changes in NK cell markers following the administration of JTT, as well as the herb-drug interaction involving CYPs and P-gp. The points raised are academically significant and have provided valuable insights into my research. Furthermore, I would like to study this field in a clinical setting. I would also welcome the opportunity to discuss or exchange information in this field moving forward. Thank you for your continued support and attention to this matter.

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