RESEARCH ARTICLE

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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

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Abstract

Background: Fatigue is an immune-related adverse event (irAE) associated with immune checkpoint inhibitors (ICIs) used for cancer treatment. Chinese herbal medicines (Ho-zai) are used to treat cancer-related fatigue. However, no interactions between ICIs and Ho-zai have been reported. Herein, we investigated the risk of irAEs associated with the concomitant use of ICIs and Ho-zai. **Methods:** We extracted data of patients who used ICI and Ho-zai from the Japanese Adverse Event Reporting Database. The proportional reporting ratio (PRR) was calculated for patients using ICI, Ho-zai, or both. We focused on cases of interstitial lung disease (ILD) and colitis, which were among the most severe cases of irAEs among these patients. The shrinkage method used by the World Health Organization-Uppsala Monitoring Center was used to detect the interactions. **Results:** Of the 799,670 patients in the database, 77,219, 2060, and 92 were using ICIs, Ho-zai, and combination treatment, respectively. The ILD and colitis groups included 39,388 and 17,522 patients, respectively. ILD signals were detected for both ICIs and Ho-zai. There were 24 cases of patients treated with concomitant ICIs and Ho-zai who developed ILD. For all combinations of all ICIs and all Ho-zai, Ω_{025} was negative, which suggested no ILD-related interactions. Colitis signals were detected for ICIs except for atezolizumab, avelumab, and durvalumab. There were eight patients treated with concomitant ICI and Ho-zai who developed colitis. For all combinations of all ICIs and all Ho-zai, Ω_{025} was negative, which suggested no colitis-related interactions. **Conclusion:** To our knowledge, this is the first study to investigate interactions between ICIs and Ho-zai. Signals were detected for ILD in both ICI and Ho-zai groups, and colitis in the ICI group. However, the combined use of these treatments did not increase the risk of irAEs.

Keywords: immune-related adverse events immune checkpoint inhibitors Chinese herbal medicines

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Introduction

Fatigue commonly occurs in patients with cancer and impairs their quality of life [1]. There is no standardized treatment for fatigue; however, various intervention approaches have been attempted, including physical activity, psychosocial, psychosomatic, and pharmacological treatments [2]. In recent years, immune checkpoint inhibitors (ICIs) have been used in chemotherapy for all types of cancer beginning with the first use of nivolumab for malignant melanoma. Immune-related adverse events (irAEs) associated with the use of ICIs are known, and the most severe of these AEs include interstitial lung disease (ILD), colitis, thyroid dysfunction, and scratchiness. Furthermore, one of the most frequent irAEs is fatigue [3, 4].

The use of Chinese herbal medicines, such as Hochuikitou Hochuekkito (HET), Juzen Daihoto (JJT), and Ginsen Yoeito (NYT), for the treatment of fatigue in patients with tumors has been reported [5, 6]. These herbal medicines are called "Ho-zai" because they are effective in replenishing the deficiency in the physical strength and energy of the body and restoring the condition of the patient. Reportedly, one mechanism of action of Ho-zai involves T cells. HET has been reported to improve an inhibition of tumor-specific Th1-type cytokine production [7], JTT increases the regulatory activity of T cells by reducing the Foxp3(+) Treg population in patients with pancreatic cancer [8], and NYT has been reported to potentiate the effects of tumor vaccines via CD8+ T cells [9]. Furthermore, a study examining the T cell and cytokine-inducing effects of HET, JTT, and NYT showed that neither HET, JTT, nor NYT induced CD4+ T cells but tended to increase CD8+ T cells in a dose-dependent manner. Ho-zai has also been reported to decrease regulatory T cells in a dose-dependent manner [10]. Thus, the use of these herbal medicines for treating fatigue in patients receiving ICIs may exacerbate irAEs,

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as well as their therapeutic effects. However, to date, there are no reports on the interactions between ICIs and Ho-zai.

The Pharmaceuticals and Medical Devices Agency collects post-marketing spontaneous AE reports and makes them publicly available via the Japanese Adverse Drug Event Report (JADER) database. JADER is a database that contains a case list table with basic patient information such as sex and age; a drug information table with details of the generic name and start and end date of administration; an AE table with information regarding the name, outcome, and onset date of the AE; and an underlying disease table with the underlying disease and other information. Recently, type 1 diabetes has been reported to be associated with ICI administration [11] and irAEs [12] in the JADER database. Herein, we used JADER to investigate the possible effects of Ho-zai used for fatigue on irAEs.

Materials and Methods

Analysis tables and extraction of target patient data

Data was extracted from the JADER database from April 2004 to November 2022 [13]. The drug information table classifies administered drugs as suspected drugs, concomitant drugs, and interactions according to their involvement in AEs. In this study, suspected drugs to be responsible for AEs were included in the analysis. The ICIs included in this study were nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, and ipilimumab, all of which are approved in Japan. Because ipilimumab is sometimes used in combination with nivolumab, the combination group was defined as the nivolumab plus ipilimumab combination group. The herbal medicines used in this study were HET, JJT, and NYT. Cases in which the drug name was not included in the drug information table were excluded.

The irAEs considered relevant for patients who received ICIs and were admitted to the intensive care unit included respiratory diseases, colitis, and metabolic diseases [14]. Metabolic diseases included renal failure, adrenocortical insufficiency, hyponatremia, and thrombotic microangiopathies. Because all these diseases were present in a small number of cases, we chose to focus on interstitial lung disease (ILD) and colitis in this study.

The JADER AE terms are based on the basic definitions in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use International Dictionary for Regulatory Activities/ Japanese version (Medical Dictionary for Regulatory Activities/Japanese version, hereafter MedDRA). In this study, ILD and colitis of the MedDRA Standardized MedDRA Queries (SMQ) of MedDRA Ver. 25.1 were used. The case lists, drug information, and AE tables were combined into a single file and used as tables for analysis.

Signal analysis for ILD and colitis

The proportional reporting ratio (PRR) [15] was used to detect signals related to ILD and colitis. The following equations were used for calculating PRR and χ^2. In this study, PRR≥2, χ^2≥4, and N11≥3 were considered as a signal.

$$PRR = \frac{(N_{11}/N_{1+})}{(N_{01}/N_{0+})} \quad (1)$$

$$\chi^2 = \frac{n_{+++} \times (|N_{11} \times N_{00} - N_{10} \times N_{01}| - n_{+++}/2)^2}{N_{1+} \times N_{+1} \times N_{0+} \times N_{+0}} \quad (2)$$

Drug D1: N11 = n111 + n101, N00 = n000 + n010, N10 = n110+ n100, N01 = n001 + n011, N1+ = n11++ n10+, N+1 = n++1, N0+ = n00+ + n01+, N+0 = n++0.

Drug D2: N11 = n111 + n011, N00 = n000 + n100, N10 = n110+ n010, N01 = n001 + n101, N1+ = n11++ n01+, N+1 = n++1, N0+ = n00+ + n10+, N+0 = n++0.

Signal analysis of drug-drug interactions

We used the Ω shrinkage measure model [16] for signal detection of drug–drug interactions. This method is based on a measure calculated as the ratio of the observed reporting ratio of the adverse event (AE) associated with the combination of two drugs and its expected value. Further, this model is used by the Uppsala Monitoring Center (UMC) and the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring for signal analysis of drug–drug interactions. The Ω shrinkage measure prepares a 4 × 2 contingency table when AEs are considered in combination, when each AE is used alone, and when all other drugs are used; and the signal is obtained by dividing the observed value by the expected value. The detailed method of calculating the signal is shown in Equation 4. $\Omega_{025} > 0$ was used as the threshold to screen for signals associated with a two-drug combination.

$$\Omega = log_2 \frac{n_{111} + 0.5}{E_{111} + 0.5} \quad (3)$$

$$\Omega_{025} = \Omega - \frac{\Phi(0.975)}{log_2 \sqrt{n111}} \quad (4)$$

n111: reported number of AEs associated with a targeted two-drug combination.

E111: expected number of AEs associated with the targeted two-drug combination.

Φ (0.975) was 97.5% of the standard normal distribution.

Statistical analysis

JMP13.0 (SAS Institute Inc., Cary, NC, USA) was used for the all statistical analyses.

Results

Of the 799,670 patients registered in the JADER database, 77,219 were in the ICI group, 2060 in the Ho-zai group, and 92 in the combination group. The ILD group consisted of 39,388 patients and the colitis group consisted of 17,522 patients, respectively.

Colitis

Colitis signals were detected with ICI, except for atezolizumab, avelumab, and durvalumab (Table 1). There were eight cases of patients treated with ICIs and Ho-zai who developed colitis. The combinations included one case each for nivolumab+ipilimumab+JJY, nivolumab+JJY, pembrolizumab+JJY, and pembrolizumab+NYT, and

Table 1. ILD and Colitis Signals were Detected with each Drug, all ICIs, and all Ho-zai

Drug Name	ILD	Other	PRR	χ^2	Colitis	Other	PRR	χ^2
Atezolizumab	673	4062	2.92	875.42	200	4,535	1.94	90.88
Avelumab	20	424	0.91	0.09	29	415	2.98	37.05
Durvalumab	1440	1180	11.54	14042.63	30	2,590	0.52	12.94
Ipilimumab	34	364	1.74	10.37	79	319	9.1	571.13
Nivolumab	2270	7391	5	7198.01	636	9,025	3.08	878.12
Pembrolizumab	2194	8909	4.19	5288.11	563	10,540	2.36	434.26
Nivolumab+ipilimumab	1250	7008	3.14	1855.72	810	7,448	4.64	2255.63
All ICIs	7881	29338	5.12	22005.71	2347	34,872	3.17	3081.9
HET	102	931	2.01	53.04	35	998	1.55	6.37
JJT	90	748	2.18	59.32	21	817	1.14	0.25
NYT	24	165	2.58	22.76	6	183	1.45	0.46
All Ho-zai	216	1844	2.14	135.15	62	1,998	1.37	6.08

ICI, Immune checkpoint inhibitors; JJT, Juzen Daihoto; NYT, Ginsen Yoeito; HET, Hochuekkito; Ho-zai, JJT+NYT+HET

Table 2. Ω_{025} on Colitis with ICIs and Ho-zai

Drug Name	Colitis	Other	Ω_{025}
Nivolumab+HET	4	23	-0.52
Nivolumab+JJY	1	8	ND
Nivolumab+ipilimumab+JJY	1	5	ND
Pembrolizumab+JJY	1	16	ND
Pembrolizumab+NYT	1	5	ND
All ICIs+All Ho-zai	8	84	-0.26

ND, not detected; ICI, Immune checkpoint inhibitors; JJT, Juzen Daihoto; NYT, Ginsen Yoeito; HET, Hochuikitou Hochuekkito; Ho-zai, JJT+NYT+HET

Table 3. Ω_{025} on ILD with ICIs and Ho-zai

Drug Name	ILD	Other	Ω_{025}
Atezolizumab+HET	1	2	ND
Atezolizumab+JJT	1	0	ND
Atezolizumab+NYT	1	0	ND
Nivolumab+HET	9	18	-0.21
Nivolumab+JJT	2	7	-1.91
Nivolumab+NYT	2	3	-1.28
Pembrolizumab +HET	2	3	-1.08
Pembrolizumab+JJT	3	14	-1.44
Pembrolizumab+NYT	3	3	-0.23
All ICIs+All Ho-zai	24	68	-0.3

ND, not detected; ICI, Immune checkpoint inhibitors; JJT, Juzen Daihoto; NYT, Ginsen Yoeito; HET, Hochuekkito; Ho-zai, Standardize the order to HET→JJT→NYT.

nivolumab+HET in four cases. Ω_{025} was not detectable for nivolumab+ipilimumab+JJY, nivolumab+JJY, pembrolizumab+JJY, and pembrolizumab+NYT. For each nivolumab+HET, the combination of all ICIs and all Ho-zai, Ω_{025} was negative (Table 2).

ILD

ILD signals were detected for each drug, ICI, and Ho-zai (Table 1). There were 24 cases of patients treated with ICIs and Ho-zai who developed ILD. The combinations were atezolizumab+JJT in one case, atezolizumab+NYT in one case, atezolizumab+HET in one case, nivolumab+JJT in two cases, nivolumab+NYT in two cases, nivolumab+HET in nine cases, pembrolizumab+JJT in three cases, pembrolizumab+NYT three cases, and pembrolizumab+HET in two cases. Ω_{025} was not detectable for atezolizumab with each Ho-zai. For each of the other drug combinations, the combination of all ICIs and all Ho-zai, Ω_{025} was negative (Table 3).

Discussion

To our knowledge, this is the first study to investigate the interaction between ICIs and Ho-zai. Signals were detected for ILD in both the ICI and Ho-zai groups and for colitis in the ICI group. However, the combined use of these treatments did not increase the risk of irAEs.

Fatigue commonly occurs in patients with cancer and those undergoing cancer treatment. Ho-zai has been shown to effectively alleviate this fatigue [5, 6]. In patients receiving ICIs, fatigue is a symptom of serious AEs, such as hypoadrenalism, hypothyroidism, and myasthenia gravis. This study suggests that Ho-zai may not pose an additional risk when used concurrently with ICIs, which can be valuable for managing such events.

Ho-zai is known for activating cytotoxic T cells and reducing regulatory T cells. Additionally, the mechanism of action of CTLA-4 inhibitors is also understood to involve the activation of cytotoxic T cells and the reduction of regulatory T cells [17]. Furthermore, the combination of CTLA-4 inhibitors with PD-1 antibodies is expected to enhance response rates and is currently used in clinical practice [18]. The combination of HET and PD-1 inhibitors was found to suppress tumor growth and increase cytotoxic T lymphocytes and natural killer cells in MC38 colon cancer model mice. The combination of Ho-zai with ICIs suggests the potential enhancement of anti-cancer immune activity [19]. Conversely, it has been reported that the incidence of irAEs, including ILD and colitis, is higher when CTLA-4 inhibitors and PD-1/*PD-L1* antibodies are used in combination than when they

are used individually [20, 21, 22].

However, in this study, the combination of ICI and Ho-zai did not increase the risk of ILD or colitis. When ipilimumab was administered at 10 mg/kg or 3 mg/kg for unresectable stage III or IV melanoma, it was reported that colitis had a higher incidence when administered at 10 mg/kg, suggesting a dose-dependent relationship [23]. Therefore, it is suggested that the clinical dose of Ho-zai may not be sufficient to induce colitis. Additionally the incidence of irAE-related lung disorders and colitis varies among different tumor types, with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) having a higher incidence of lung disorders compared to melanoma, and melanoma having a higher incidence of colitis compared to the other two diseases [24, 25]. In this study, the information in the JADER database about the underlying diseases was limited; hence, the patient backgrounds were not considered, and it is possible that the bias in underlying diseases may have affected the results.

Although there have been reports of ILD caused by traditional Chinese medicine (TCM), all of them contained ou-gon, which is considered to be the cause of allergy [26, 27]. Regarding traditional Chinese medicine-induced colitis, phlebosclerotic colitis has been reported, which is considered to be caused by geniposide found in the gardenia fruit [28, 29]. However, Ho-zai used in this study did not contain ou-gon or the gardenia fruit, and it was considered that Ho-zai did not increase the risk of ILD or colitis in this study.

The present study has several limitations. First, it only considered two particularly urgent irAEs, and there may be interactions for other irAEs. Second, spontaneous reporting databases are generally associated with reporting biases, such as underreporting [30, 31], data loss [30], increased reporting rates for topical AEs (notoriety and ripple effects) [30], and duplication of reports [31]. Therefore, caution is warranted when interpreting the results obtained from the JADER database.

The interactions between ICIs and herbal medicines are not only limited to irAEs but may also have an impact on the therapeutic efficacy of the drugs. In the future, we will measure the treatment effect and include other irAEs using real-world data.

Author Contribution Statement

Toru Koshiishi and Koichi Yoshimoto contributed to the study conceptualization. Toru Koshiishi contributed to data analysis and interpretation, and also wrote the manuscript. Koichi Yoshimoto contributed to the manuscript drafting. Nanao Nishioka contributed to revising the manuscript. All authors critically reviewed and revised the manuscript draft and approved the final version for submission.

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If it was approved by any scientific Body/ if it is part of an approved student thesis

This study did not require the approval of an ethics committee, as it involved the secondary use of existing, anonymized data from publicly accessible databases. No specific scientific body oversaw the conduct of this research; however, all procedures were carried out in accordance with relevant guidelines and regulations.

How the ethical issue was handled (name the ethical committee that approved the research)

This study does not fall under the 'Code of Ethics for Medical Research Involving Human Subjects' as it exclusively uses publicly available, anonymized data obtained from JADER. Therefore, it was determined that Institutional Review Board approval was not required.

Availability of data (if apply to your research)

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Any conflict of interest

The authors declare no conflict of interest related to the study.

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