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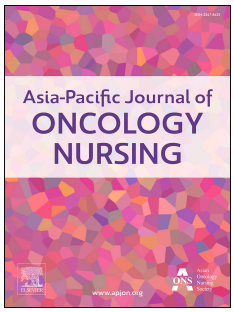

An Exploratory Cross-sectional Study of Immune Checkpoint Inhibitors and Immuno-related Adverse Events: Knowledge and Influencing Factors among Japanese Oncology Nurses

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An Exploratory Cross-sectional Study of Immune Checkpoint Inhibitors and Immuno-related Adverse Events: Knowledge and Influencing Factors among Japanese Oncology Nurses

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An Exploratory Cross-sectional Study of Immune Checkpoint Inhibitors and Immuno-related Adverse Events: Knowledge and Influencing Factors among Japanese Oncology Nurses

Abstract

Objective: Adequate knowledge of immune checkpoint inhibitors (ICIs) and associated immune-related adverse events (irAEs) is essential for managing such events. However, the level of knowledge among Japanese nurses remains unclear. This study aimed to investigate the current status of ICIs and irAE knowledge and the factors influencing them, among outpatient nurses caring for patients undergoing ICI treatment.

Methods: An exploratory cross-sectional study was conducted at 450 facilities nationwide. Participants completed a self-administered online questionnaire consisting of three parts, measuring personal and environmental attributes and awareness and knowledge of irAEs. Questions were based on multiple literature sources and were evaluated and validated by medical oncologists and certified oncology nurses.

Results: A total of 196 (response rate: 36%) nurses responded to the survey at 109 facilities (valid responses: 192; rate: 35%). The correct response rate was 27.6% for questions on general ICI knowledge and 15.6% for general irAE knowledge. Questions on pulmonary dysfunction had the highest correct response rate (41.7%), while those on neuromuscular/joint dysfunction had the lowest (1%). The mean correct response rates were 76% for general knowledge and 48.1% for ICI-specific knowledge. Multiple regression analysis showed that the most influential factor was participants' study schedule ($p<.05$).

Conclusions: There is room for nurses to acquire additional knowledge about ICIs and irAEs. The use of patient education tools and a study schedule significantly increased knowledge scores. Further research is needed to identify when and how to provide nurses with opportunities to acquire additional ICI and irAE-related knowledge.

1. Introduction

Cancer has been the leading cause of mortality in Japan since 1981, causing approximately 380,000 deaths per year in 2020.[1] However, the five-year relative survival rate has exceeded 60% since 2009.[2]

Approaches to cancer treatment have also been changing in Japan. The number of domestic outpatients with malignant neoplasms now exceeds the number of inpatients, a trend that has increased in recent years.[3] This change is due to a variety of factors currently occurring in Japan, including the limited number of beds available at inpatient facilities, the promotion of home care, and advances in cancer drug therapy.

Oncology pharmacotherapy is diversifying with the introduction of cytotoxic anticancer agents, molecular targeted agents, and immune checkpoint inhibitors (ICIs), all of which have completely different mechanisms from conventional immunotherapy.[4-8] As of 2019, three ICIs had either been approved or were undergoing clinical trials in Japan: CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors. These have since been approved for nine types of cancer,[4] and clinical trials with these ICIs are being conducted for more than 25 cancer types. These trials are expected to result in additional indications for many cancer types and stages.

The mode of action behind immune-related adverse events (irAEs) caused by ICI therapy remains unknown. It is also unclear why some patients experience irAEs, while others do not. Managing irAEs is different from managing the side effects of cytotoxic anticancer drug therapy. This is because irAEs appear in various forms and can, theoretically, occur anywhere in the body. Moreover, it is difficult to predict when they will appear, and delays in appropriate response and treatment can be fatal.[4,9,10] However, there is no established treatment or supportive care beyond the use of steroids.[4] Additionally, recent studies have shown that the risk of

mortality and disease progression is reduced when irAEs occur.[11,12] Thus, recognizing and managing irAEs is a critical factor for ensuring that patients continue to receive the treatment they require.

Against this background, nurses must have adequate knowledge of ICI treatment and any associated irAEs.[13] However, although nurses must possess knowledge related to the medications used for each patient, their actual acquisition of such knowledge remains insufficient.[14,15] According to the results of a survey of 160 nurses involved in clinical practice and education in various fields, nurses are aware of the need to provide nursing care based on evidence-based knowledge; however, they have difficulty translating this knowledge into practice.[16]

As ICI therapy is likely to become a mainstream cancer treatment in the near future, nurses need to acquire knowledge about ICI therapy and irAEs. However, the current status of nurses' knowledge about ICIs and irAEs and the recognition of their importance in Japan have not yet been clarified. Furthermore, globally, there is no research or questionnaire assessing ICI and irAE knowledge. At present, supportive care for adverse events associated with ICI therapy has not been established. As such, it is vital for nurses to have appropriate knowledge regarding irAEs to ensure early detection and treatment, thereby reducing distress among patients and their families. An appropriate level of knowledge is also needed to ensure that effective treatment can be safely continued and sufficient therapeutic effects are realized.

This study aimed to test the following research hypotheses by examining knowledge of ICIs and irAEs—and the factors affecting that knowledge—among outpatient nurses involved in the care of patients undergoing ICI treatment in Japan. This study seeks to contribute to the field by analyzing the hypotheses based on a conceptual diagram of knowledge, attributes, and awareness of irAEs (Figure). Since no theoretical framework existed, the conceptual diagram

was originally schematized by the author. Knowledge of ICIs and irAEs is associated with personal attributes and environmental characteristics. Awareness of irAEs is associated with personal attributes, environmental characteristics, and knowledge of ICIs and irAEs. Personal attributes are in turn associated with environmental characteristics.

Hypothesis 1: Nurses who study ICIs and irAEs gain adequate knowledge compared to those who do not.

Hypothesis 2: Knowledge of ICIs and irAEs among nurses involved in ICI treatment would be associated with nurses' personal attributes, such as irAE management training participants, providing opportunities for learning about irAEs, and the number of ICI-administered patients involved in care to date. A null hypothesis will be tested to the effect that there is no association between knowledge of irAEs and nurses' personal attributes, such as irAE management training participants, providing opportunities for learning about irAEs, and the number of ICI-administered patients involved in care.

Hypothesis 3: Knowledge of ICIs and irAEs among nurses involved in ICI treatment would be associated between two groups of nurses' environmental characteristics, such as the presence of an in-house multidisciplinary team, certified cancer-related personnel, and an ICI-specific questionnaire in the facility. A null hypothesis will be tested to the effect that there is no association between knowledge of irAEs and nurses' environmental characteristics, such as the presence of an in-house multidisciplinary team, certified cancer-related personnel, and an ICI-specific questionnaire in the facility.

2. Methods

2.1 Design

This was an exploratory cross-sectional study using an internet-based self-administered questionnaire.

2.2 Setting

A total of 450 facilities in Japan were included in this study, including 447 designated comprehensive cancer centers and 86 advanced treatment hospitals that do not overlap with the designated comprehensive cancer centers.[17,18]

A research request letter, a sample questionnaire, a sample research cooperation request form for cooperating nurses, and a reply-paid postcard were sent to the head of the nursing department of the facility where the survey was conducted. The return postcards were sent by the head of the nursing department of the facility where the survey was to be conducted, with the name of the person in charge of accepting the survey and the number of possible collaborators indicated. Based on the returned postcards, a "Request for Research Cooperation Form" was mailed to the person in charge of accepting the survey at facilities that agreed to cooperate. The form included the purpose of the study and the URL and 2D code to access the Internet survey for the cooperating nurses. The research coordinator distributed this form to nurses who were involved in ICI administration nursing in the outpatient chemotherapy centers and outpatient treatment centers of gastroenterology and respiratory medicine, or similar departments, and requested their responses via the Internet.

The data collection period was from June to September 2020.

2.3 Participants

The survey targets were nurses working in departments involved in the care of patients undergoing ICI treatment at the concerned facilities. The survey did not ask whether participants held certifications, such as certified cancer chemotherapy nursing or cancer nursing specialist in

oncology.

2.4 Sample Size Calculation

The total number of items calculated for the sample size was 35, which included 10 main attribute items from the 26 attribute items considered and selected to be particularly influential on irAE management, eight awareness items (7 questions and 1 free comment), nine items testing knowledge about ICIs and irAEs, and eight items on the various types of irAEs. The required minimum sample size was set at 175, five times the number of items.[19] Assuming that the response rate will be 25%, the number of required participants was calculated to be 700 (=175/0.25). The number of facilities requested was calculated to be 281 (=70/0.25) assuming a minimum of 70 facilities and a response rate of 25%, based on the assumption that 10 nurses from one facility would respond to the survey.

2.5 Questionnaire

2.5.1 Test of ICI and irAE Knowledge

Questions related to basic knowledge of ICIs and irAEs were based on the Cancer Immunotherapy Guidelines (second edition),[4] National Comprehensive Cancer Network guidelines,[6] and previous studies.[8,17,18.20-26] The survey consisted of ten items meant to extract participants' basic knowledge about ICIs and irAEs, specific symptoms of irAEs by area, frequency of occurrence, severity (mortality rate), and urgency as well as specific symptom measures and non-steroidal treatment. Knowledge scores were based on whether participants answered the true/false questions correctly.

Nine oncologists, pulmonary physicians, oncology certificated nurse specialists, and certified cancer chemotherapy nurses were asked to evaluate the content validity of the ICI and irAE knowledge test in terms of appropriateness, difficulty, necessity, and modifications. The

appropriateness, difficulty, and necessity of each item were rated on a three-point Likert-type scale (3, *high*; 2, *neither*; 1, *low*); the mean scores were 2.4, 2.1, and 2.7, respectively. Modifications were made based on these results.

A pilot survey of the modified ICI and irAE knowledge test was conducted with three nurses working at a designated comprehensive cancer center. The items were then re-examined and finalized.

2.5.2 Awareness of irAEs

Eight questions related to irAE awareness were set by referring to the item on side effects in the "31 items of nursing practice for cancer patients undergoing chemotherapy,"[14] replacing chemotherapy and its associated side effects with ICIs and irAEs, respectively. The response format was a five-point Likert scale.

The Transtheoretical Model (TTM)[27] was applied to set up the answers for question 7, "plan to learn about irAEs."

2.5.3 Attributes (Personal Attributes and Environmental Characteristics)

A total of 26 items were asked based on multiple sources, including 20 items related to personal attributes and six related to environmental characteristics that are considered influential in the acquisition of cancer care expertise. Participants were asked to select applicable items or write freely.

2.6 Data Analysis

We performed a variance, correlation coefficient, and multiple regression analysis with attributes (personal attributes and environmental characteristics) and awareness of irAEs (7 questions and 1 free comment) as the independent variables and irAE knowledge test scores as the dependent variable.

The knowledge test score was calculated as one point for each of the 41 questions in the ten domains, resulting in a total of 41 points for the knowledge test score. Additionally, each of the irAE question options (Q3 through Q10: total 32 options) was divided into two categories (except Q1 and Q2, which were ICI-related questions): knowledge required for general cancer nursing (12 options) and knowledge required for nursing specific to ICI (20 options), with one point each for a total of 32 points. The average percentage of correct answers was calculated. SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) was used for analysis, and the significance level was set at .05%.

In accordance with the hypothesis, the knowledge test scores on ICIs and irAEs were used as the dependent variable and the other variables were used as independent variables to examine the influencing factors.

2.7 Ethical Considerations

This study was conducted after obtaining approval from the Research Ethics Review Committee of an international university (approval no. 20-A018). All participants provided written informed consent.

3. Results

3.1 The Number of Survey Participants and Response Rate

We sent a letter in advance to 281 nurse directors at the target facilities, which were randomly selected from 450 eligible facilities, requesting their participation. Nurse directors approached nurses who were involved in ICI administration nursing in the outpatient department, where cancer patients with indications for ICIs are treated. We sent 538 request letters to 109 facilities (63%) that agreed to cooperate (38%). We received responses from 196 (36%), and 192

valid responses were obtained (valid response rate: 35%). Table 1 summarizes the basic attributes of the participants.

3.2 General Data

Table 1 summarizes the basic attributes of the participants.

3.3 Nurses` Knowledge Level

Table 2 presents the results of the ICI and irAE knowledge test. The mean score was 26.2 out of 41 (63.9% correct, standard deviation (SD) 5.48), and the median score was 26.5. Among the individual questions, nine questions on ICI and irAE general knowledge were excluded because they combined the two types of knowledge, preventing individual measurement of ICI- and irAE-specific knowledge. The remaining questions were divided into ICI- or irAE-specific knowledge (20 questions, “a” in Table 2) and general knowledge necessary for cancer nursing (12 questions, “b” in Table 2). The average percentage of correct answers for general knowledge of cancer nursing was higher than the average percentage of total correct answers, while the average percentage of correct answers for ICI-specific knowledge was lower. This was also true for the percentage of correct answers for each of the irAE topics; the percentage of correct answers was higher for the general knowledge questions and lower for the questions with more ICI-specific options. The irAE topics that exceeded the average percentage of correct answers for all questions were pulmonary dysfunction (41.7%) and hepatic dysfunction (27.1%). The reliability coefficient (Cronbach’s alpha) for the knowledge test was 0.79.

3.4 Influencing Factors: Single Factor Analysis

3.4.1 Personal Attributes and Environmental Characteristics Associated with Knowledge Test Scores

The relationships between the knowledge test scores and the nominal variables of personal

attributes and environmental characteristics are shown in Table 3. The significant personal attributes were the number of beds, current department, certification held, highest level of nursing educational background, academic society affiliation, participation in irAE management training, experience with currently predictable irAEs, experience with currently unpredictable irAEs, existence of free self-study, existence of paid self-study, and affiliation with ICI-related multidisciplinary teams in the hospital. The significant environmental characteristics were the presence of certified personnel in the hospital, use of an ICI-specific questionnaire, and presence of a patient education tool ($p < .05$).

The continuous variables of personal attributes and environmental characteristics that were correlated with ICI and irAE knowledge test scores by correlation coefficients were significantly different by years of experience in cancer nursing, number of certifications held, number of academic society affiliations, number of free self-study opportunities/modes, number of paid self-study opportunities/modes, number of in-hospital certified personnel, number of irAE confirmation tools, and number of patient education tools. The correlation coefficients were weak, ranging from 0.2 to 0.4.

The ICI and irAE knowledge test scores for irAE management training participants were significantly higher, with a mean score of 28.5 (SD 4.80) and a median score of 29, than the scores of participants who had not participated in such training.

In terms of the mean and median scores for the number of self-learning opportunities/modes, there was a difference in scores between the “free” group with two or fewer opportunities/modes and the “paid” group with three or more opportunities/modes. There was also a difference between the paid group with one or no opportunities/modes and the paid group with two or more opportunities/modes. Therefore, we set up groups according to the number of

items for which a difference in scores was observed: two or fewer and three or more for the free group, and one or more for the paid group. We then compared these groups using Mann–Whitney U tests. The results showed that there was a significant difference in knowledge depending on the number of free self-study opportunities/modes (between two or fewer and three or more [p=.000]) and the number of paid self-study opportunities/modes (between one or no opportunities and two or more [p=.004]).

Those with fewer than five years of clinical experience (n=4) scored higher on the knowledge test (mean 30.5 SD 5.74, median 31). However, those with fewer than five years of oncology nursing experience (n=44, mean 18 years of clinical experience) scored lower (mean 23.7 SD 7.84, median 21). Although there was no significant difference in knowledge test scores for either years of clinical experience or of oncology nursing experience, correct responses were higher in the group with six or more years of clinical experience than in that with one to five years of experience. Scores were also higher for those with oncology nursing experience than for those without.

Based on the results of the above analysis, the personal attributes and environmental characteristics that were related or correlated with the knowledge test scores were certifications held, academic society affiliation, free self-learning opportunities/media, irAE confirmation tools, and patient education tools.

Regarding learning status, participants with previously predicted and unpredicted irAEs used multiple self-learning opportunities/modes. Furthermore, more than two-thirds of them indicated that they were already engaged in learning (more than six months and six months or under).

3.4.2 Examination of Awareness of irAEs as Related to Knowledge Test Scores

The relationships between ICI and irAE knowledge test scores and awareness of irAEs are shown in Table 4. Free comments (n=23) on the awareness of irAEs are shown in Table 5; the relationships between ICI and irAE knowledge test scores could not be analyzed due to insufficient data. The results showed that independence was dismissed in knowledge test scores and awareness of irAEs, with "calling on oneself to identify irAEs," "patient education on the purpose of irAE prevention and coping behaviors is important," "improving knowledge of the antitumor effects and adverse events of the drugs administered to each patient is important," and "learning schedule for irAEs" were significantly different ($p < .05$). Hence, an association was observed.

No association was found between "early detection of irAEs is the physician's role" and knowledge test scores. There was a significant difference between the "agree" and "neither agree nor disagree" groups (multiple comparison method). The "neither agree nor disagree" group had higher knowledge test scores. "It is the physician's role" and "it is not the physician's role" groups had lower scores than the "neither agree nor disagree" group.

The "plan to learn" item of the awareness of irAE variable was the most relevant to knowledge test scores on ICIs and irAEs.

3.4.3 Influencing Factors: Multiple Regression Analysis

The multiple linear regression analysis results are shown in Table 6. We used a forced imputation method to examine the relationship between ICI and irAE knowledge test scores and the significant variables of attribute and irAE awareness.

Therefore, the standardized coefficients (β) of each of the variables in the questionnaire showed that "plan to learn" and "certifications held" influenced the knowledge test scores, but the significant probability was $p < .05$ for "plan to learn."

4. Discussion

In this section, we examine the relationship between the items based on the obtained results and discuss future strategies for nurses to acquire knowledge.

4.1 Characteristics of the Target Population

More than 70% of the participants were nurses in their 40s or older and working in medium-sized or larger facilities. This sample is slightly older than the general population of nurses in Japan, where just under 50% of hospital nurses are in their 40s or older.[28] More than 70% of the nurses had experience of caring for more than 21 patients on ICI therapy, and nearly 90% of the nurses worked in outpatient chemotherapy units, suggesting that this is a group involved in cancer drug therapy daily.

4.2 Nurses` Knowledge Level

As described earlier, the reliability coefficient (Cronbach's alpha) for the knowledge test was 0.79. Therefore, the knowledge test used in this study remained reliable, and we believe it was appropriate for measuring nurses' knowledge on ICIs and irAEs in this aspect. Additionally, in terms of awareness of irAEs, nearly 35% of the participants who answered "already learning (more than six months)" to the question "plan to learn about irAEs" scored significantly higher (mean 29.07, SD 3.95, median 30) than who did not. This suggests that the test was an appropriate measure of the knowledge of those accessing learning opportunities.

As per the result shown, in each of the irAE categories, only two categories had a higher-than-average percentage of all questions answered correctly on the knowledge test: pulmonary dysfunction (41.7%) and hepatic dysfunction (27.1%). We believe that the pulmonary dysfunction knowledge score was the highest because of rising awareness among nurses about

reports of deaths because of the interstitial pulmonary dysfunction associated with ICI treatment and also because the mortality rate of drug-induced pulmonary dysfunction due to cancer drug therapy in Japan is higher than that in other countries.[30] Based on the above, the probability that nurses have been involved in the care of patients with cancer who develop drug-induced pulmonary dysfunction is high, so it can be inferred that nurses are aware of this problem.

In contrast, the knowledge scores for dermatological dysfunction (47.2%), neurologic/musculoskeletal dysfunction (39.2%), endocrine dysfunction (46.3%), and cardiac dysfunction (48.3%) were below the average percentage of each question answered correctly. In these areas, a lack of penetration of disease-specific knowledge may be a factor. This is because the incidence of irAE itself is in the single digits, and a variety of diseases are included in this area. Although endocrine dysfunction also includes a variety of diseases, 56% of the participants correctly answered, "(c.) thyroid dysfunction is the least frequent endocrine dysfunction among irAEs (incorrect)."[4,6,7,20–22] It is assumed that the participants were aware of thyroid dysfunction, which is relatively frequent among irAEs; this led to the acquisition of knowledge. For cardiac dysfunction, the result indicates that the acquisition of knowledge about the general cardiovascular system is also an issue.

The distinctive results showed that correct response rates for gastrointestinal and dermatological dysfunction, which are considered to occur more frequently among irAEs,[4,6,7,21–23] were lower than those for neurologic/musculoskeletal dysfunction. The incidence of gastrointestinal dysfunction caused by ICIs is estimated to be 30%–40%, and fatalities, such as those resulting from intestinal perforation, have been reported. Unlike gastrointestinal disorders caused by cytotoxic anticancer drugs, the use of antidiarrheal agents may delay treatment for irAEs and cause serious complications.[4,6–8] However, the item-specific correct response rate was

low.

In this knowledge test, questions related to general clinical symptoms and care were avoided as much as possible because the target audience was nurses who were already engaged in clinical practice. The test was composed of questions related to specialized knowledge of ICIs and irAEs as well as specific clinical symptoms and responses. Furthermore, the percentage of correct answers to irAE-specific questions, such as the frequency, timing, severity, and grade of irAEs, was low. Therefore, it can be considered that the participants lacked knowledge of ICIs and irAEs.

According to the above data, we analyzed that nurses caring for cancer patients undergoing ICI treatment need to further improve their basic knowledge of ICIs and irAEs especially the frequency of incidence or are prone to become severe irAEs. Furthermore, the study found that nurses urgently need to acquire knowledge about low occurrence fatal irAEs. For preventing irAEs, it is significant to first know the immune-toxicity spectrum[13], especially for early detection of irAEs, which is one of the most significant roles of nurses caring for patients undergoing ICI treatment.

4.3 Influencing Factors of the Knowledge Test Scores and Attributes

The ICI and irAE knowledge test scores for irAE management training participants were significantly higher than the scores of participants who had not participated in such training programs. Although participation in training programs is an effective means of acquiring knowledge, further intervention studies are needed because nurses who already possess the required knowledge may participate in training programs to acquire further knowledge.

Nurses who engaged in self-learning had significantly higher knowledge test scores than those who did not. On the contrary, there was no significant difference in knowledge test scores

when only a single learning opportunity or mode was accessed, and the knowledge test scores were significantly higher when three or more free learning opportunities or modes were accessed or two or more paid learning opportunities or modes were accessed. This suggests that the use of multiple self-learning systems possibly in combination with a paid system will enable effective learning for knowledge acquisition.

Furthermore, the knowledge test scores were significantly higher for participants who answered "*yes*" to the questions on experience with predictable or unpredictable irAEs than for those who answered "*no*" to predictable irAEs. In other words, those who indicated that they had experience with predictable or unpredictable irAEs had already acquired knowledge of irAEs and were likely to provide nursing care with awareness of irAEs.

The results of this study showed a trend in terms of the extent of experience and institutional attributes of the target population; working in a specialized comprehensive cancer center did not significantly affect the level of expertise. Additionally, nurses working in general hospitals and university hospitals maintain their knowledge due to diverse associations. Although the sample size was small, the knowledge test scores were higher in those with fewer than five years of clinical experience (n=4; mean 30.5, SD 5.74, median 31). We can assume that after they graduated from a nursing educational institution, they were assigned to an outpatient chemotherapy center or outpatient department as nurses with recently updated knowledge.

There was no significant difference in knowledge test scores according to the number of years of clinical experience or the number of years of oncology nursing experience. However, the percentage of correct answers increased with the number of years of clinical experience. There was also no significant difference in knowledge test scores according to the number of years of experience working in comprehensive cancer centers or chemotherapy centers.

Furthermore, those with six to ten years of experience working in comprehensive cancer centers had the lowest scores compared to the overall group without work experience in comprehensive cancers. Additionally, the scores of those with fewer than five years of oncology nursing experience (n=44; mean 18 years of clinical experience) were the lowest (mean 23.7, SD 7.84, median 21). These results suggest that nurses' knowledge acquisition is highly influenced by the environment in which they are placed, for instance the availability of ICI-specific questionnaires and patient education tools.

Nurses using ICI-specific questionnaires, irAE confirmation tool, and patient education tool had significantly higher knowledge test scores than those who did not. As nurses use these tools to make direct explanations to patients, it is highly likely that nurses learn about irAEs ahead of time, before explaining them to patients, or that they learn about them through such patient explanations. This will likely be an opportunity to acquire knowledge not only for nurses with limited experience, as mentioned earlier, but also for nurses involved in such situations.

4.4 Influencing Factors of Knowledge and Awareness of irAEs

Participants who answered "*agree* (it is important)" to the questions on the importance of talking to patients, educating patients, and improving their own knowledge had significantly higher knowledge test scores. It can be assumed that a high knowledge test score is a result of learning, which further results in confidence in nursing. It can also be assumed that nurses select and implement appropriate nursing care based on specific information, theories, and methods; that is, the patient is approached and the irAE is confirmed.[29]

There was a significant difference in the response to the question on whether early detection of irAEs is the physician's responsibility when an in-house ICI-related multidisciplinary team exists. Moreover, the presence of qualified personnel in the hospital, or in

a nurse's own department, was significantly related to nurses talking to patients themselves; however, no significant relationship was found with "plan to learn."

4.5 Future Suggestions for Knowledge Acquisition

Regarding the question on "plan to learn" in the questions on awareness of irAEs, the transtheoretical model (TTM)[32] was used. The finding indicates that further research is needed to determine the kind of approach that should be adopted in the future to educate the 30% who were in the contemplation and precontemplation stages. In this study, nearly 95% of the nurses indicated that they used free learning opportunities/modes for self-improvement, including seminars, lectures, training sessions, conference-produced materials, and e-learning. The TTM considers the use of these modes to be part of the preparation stage.

Additionally, computerized interactive interventions may lead to significant results in terms of behavior changes.[27] Digital tools such as apps and social networking sites, which were among the answer choices for learning opportunities/modes currently used, were not mentioned in the survey results. However, the participants freely stated that they would learn if online learning materials and tools were available or if they had the time and schedule flexibility to participate. Thus, it is possible that on-demand digital tools that are interactive and can be completed at any pace, according to one's own convenience, would be useful.

4.6 Limitations and Future Challenges

As mentioned earlier, the content of the irAE knowledge test was extracted from the Cancer Immunotherapy Guidelines[4] and relevant literature.[6-8,20-22,31,32] The test was then confirmed by an expert panel. However, further validation is needed to evaluate the reliability of the test as a knowledge test on ICIs and irAEs. Additionally, further research is needed to evaluate the correct response rate of this test, including validation and different target groups.

In this survey, about 90% of the participants were nurses who care for patients undergoing anticancer drug therapy in outpatient chemotherapy units or outpatient infusion centers. In the future, it will be necessary to devise recruitment methods so that more nurses who provide cancer nursing care at general outpatient clinics or best supportive care units can be included. The reason is that most patients receiving ICI treatment have intervals between administration (two to six weeks[20,21]); irAEs may occur late after the completion of treatment,[4,9,20-22] and the occurrence of irAEs may require permanent treatment for irAEs. Additionally, ICIs may be combined with other cancer drugs or radiation therapy based on new regimen approvals. The management of irAEs resulting from ICIs requires educating patients prior to treatment and providing ongoing support through multiple methods tailored to each patient.[13,31] In parallel, nurses need to know what to ask and how to respond to patients, and they must have experience and knowledge of the treatment and underlying disease so that they can distinguish complications.[33] Nurses play a role not only in preventing physical deterioration through early detection of irAEs but also in supporting patients to continue the necessary or desired treatment over the mid-to-long-term period. Considering the above, it is necessary to further verify the results of this study by conducting an additional survey that fully addresses the context of these participants.

5. Conclusion

This study revealed that there is room for nurses to acquire more knowledge about ICIs and irAEs, as ICI pharmacotherapy occupies an important position in cancer treatment.

Based on the suggestions from the study findings and in light of the above, specific consideration should be given to computerized interactive tools that are appropriate to the

nurses' stage of knowledge acquisition, to building an ICI-related multidisciplinary team or a potential substitute for such a team at hospitals, and to increasing nurses' awareness of their role in confronting patients by providing specific information on how appropriate feedback and change can lead to positive outcomes for patients. A challenge for the future is to build multiple effective knowledge acquisition opportunities through patient education tools, questionnaires, and other direct patient media and linking them to behavior change. Based on the present results, the possibility of clinical application to the acquisition of knowledge in other fields and other treatment methods should also be considered.

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Table 1. Personal Attributes ***N*=192**

Personal Attributes	Items	n	(%)
Sex	Male	8	4.2
	Female	182	94.8
	No Response	2	1
Job Title	Staff	152	79.2
	Manager	40	20.8
Age	20s	7	3.6
	30s	62	32.3
	40s	101	52.6
	50s	18	9.4
	Over 60	4	2.1
Years of clinical experience			
	5 years or less	4	2.1
	6–10 years	23	12.2
	11–15 years	33	17.6
	16–20 years	52	27.7
	21 years or more	76	40.4
Years of cancer nursing clinical experience			
	5 years or less	44	23.3
	6–10 years	46	24.3
	11–15 years	39	20.6
	15–20 years	37	19.6
	21 years or more	23	12.2
The number of qualifications held such as certified cancer chemotherapy nursing /cancer nursing specialist in oncology / others			
	0	124	64.6
	1	66	34.4
	2	2	1
Final level of nursing education			
	Nursing school	143	74.5
	Bachelor's degree	36	18.8
	Master's degree	13	6.8
Participation in irAE management training			
	Yes	60	31.3
	No	132	68.8

Abbreviation: irAE, immune-related adverse event.

Table 2. Result of ICI and irAE Knowledge Test (Q3)

***N*=192**

Question Items		Answer Options (True and False)	Separate Items		All Items			
			True *n* (%)	Average True (%)	True *n* (%)		False *n* (%)	
ICI related (4 items)	1[a]	a. ICIs release the brakes on the immune system by blocking inhibitory signals, thereby enhancing the immune response to tumors. (True)	151	(78.6)	53	(27.6)	1	(0.5)
	2[a]	b. The immune system has a gas pedal that activates the immune response and a brake that inhibits it. (True)	132	(68.8)				
	3[a]	c. The inhibitory receptors of immune checkpoint molecules are expressed on the B cells of lymphocytes. (False)	160	(83.3)				
	4[a]	d. The typical inhibitory receptors of ICIs for immune checkpoint molecules are CTLA-2, CTLA-4, PD-1, and PD-L1. (False)	81	(42.2)				
				(68.2)				
irAE related (5 items)	5[a]	a. AEs occur less frequently than with cytotoxic anticancer agents. (True)	97	(50.5)	30	(15.6)	0	(0.0)
	6[a]	b. The timing of AE onset is difficult to predict. (True)	150	(78.1)				
	7[a]	c. Adverse events may occur even after ICI administration is completed (True)	169	(88.0)				
	8[a]	d. The treatment is similar to traditional cytotoxic anticancer drug side effects. (False)	177	(92.2)				
	9[a]	e. It has been reported that the prognosis of patients who develop irAEs is better than that of patients who do not develop irAEs. (True)	67	(34.9)				
				(68.7)				
Skin dysfunction (4 items)	10[a]	a. Skin dysfunction is the most frequent and delayed adverse effect observed. (False)	105	(54.7)	11	(5.7)	28	(14.6)
	11[a]	b. Stevens–Johnson syndrome and toxic epidermal necrolysis are grade 3 or higher adverse events. (True)	133	(69.3)				
	12[a]	c. Less than 3% of adverse events are grade 3 or higher. (True)	66	(34.4)				
	13[a]	d. Severe skin dysfunction occurs in combination with other agents such as cytotoxic anticancer agents and in sequential therapy. (True)	59	(30.7)				
				(47.2)				
Gastrointestinal dysfunction (4 items)	14[a]	a. Diarrhea and colitis occur in 30~40% of patients. (True)	92	(47.9)	24	(12.5)	2	(1.0)
	15[a]	b. Treatment with antidiarrheal drugs such as loperamide hydrochloride may delay the initiation of appropriate treatment and lead to more severe disease. (True)	119	(62.0)				
	16[b]	c. Diarrhea and colitis can become severe rapidly, but they do not cause gastrointestinal perforation. (False)	187	(97.4)				
	17[a]	d. There have been reports of fatalities. (True)	105	(54.7)				
				(65.0)				
Pulmonary dysfunction (4 items)	18[a]	a. The incidence is less than 1%. (False)	175	(91.1)	80	(41.7)	1	(0.5)
	19[b]	b. May worsen in a short time. (True).	154	(80.2)				
	20[a]	c. Death has occurred in some cases. (True)	145	(75.5)				
	21[b]	d. Patients may be asymptomatic in the early stages, depending on the extent of damage and inflammation intensity. (True).	128	(66.7)				
				(73.4)				

Hepatic dysfunction (4 items)	22[b]	a. It is necessary to exclude hepatic dysfunction due to infection, drugs, or worsening of the primary disease. (True)	143	(74.5)	(75.8)	52	(27.1)	0	(0.0)
	23[b]	b. The hepatic dysfunction caused by ICI is alcoholic liver disease. (False)	190	(99.0)					
	24[b]	c. For early detection, it is necessary to periodically check hepatic function test values. (True)	175	(91.1)					
	25[a]	d. Hepatic dysfunction is observed in less than 5% of patients. (True)	74	(38.5)					
Nerve, muscle, and joint dysfunction (4 items)	26[a]	a. Neuropathy can occur at any site from central to peripheral nerves and can be severe. (False).	73	(38.0)	(39.2)	2	(1.0)	44	(22.9)
	27[a]	b. Autoimmune encephalitis, demyelinating neuropathy, myasthenia gravis, and myositis are serious irAEs that often occur early during treatment (typically up to 4 doses). (True)	66	(34.4)					
	28[a]	c. Symptom progression is often more rapid and severe than in general myasthenia gravis. (True)	108	(56.3)					
	29[a]	d. Rapid respiratory failure is also more common than in general myasthenia gravis. (True).	54	(28.1)					
Type 1 diabetes (4 items)	30[a]	a. The incidence is less than 1%. (True)	62	(32.3)	(67.8)	34	(17.7)	5	(2.6)
	31[b]	b. Type 1 diabetes does not occur in patients with a history of type 2 diabetes. (False)	184	(95.8)					
	32[b]	c. Fulminant type 1 diabetes develops hyperacutely over a few days. (True).	144	(75.0)					
	33[b]	d. Fulminant type 1 diabetes is fatal if treatment is not started immediately after onset, because blood glucose levels rise even more rapidly, regardless of the blood glucose level at the time of detection. (True)	131	(68.2)					
Endocrine dysfunction (4 items)	34[b]	a. Hypopituitarism may be followed by secondary hypoadrenalism, and in severe cases, adrenal crisis may lead to shock. (True)	112	(58.3)	(46.3)	25	(13.0)	5	(2.6)
	35[a]	b. Adrenal dysfunction often develops in the first few months of treatment. (True)	65	(33.9)					
	36[a]	c. Thyrotoxicosis is the least frequent endocrine disorder among irAEs. (False)	108	(56.3)					
	37[a]	d. Some thyroid dysfunction leads to hypothyroidism via thyrotoxicosis, while others exhibit hypothyroidism from the onset. (True)	71	(37.0)					
Cardio-vascular dysfunction (4 items)	38[a]	a. The symptoms are diverse, including asymptomatic presentation, fatal arrhythmia, and heart failure. (True)	93	(48.4)	(48.3)	36	(18.8)	12	(6.3)
	39[a]	b. The incidence of myocarditis is not high, but the fatality rate of severe cases is as high as 20%–50%. (True)	74	(38.5)					
	40[b]	c. Fulminant cardiomyopathy is a rapidly worsening condition that often results in death in a very short time. (True)	93	(48.4)					
	41[b]	d. Administration of antiarrhythmic drugs for arrhythmia associated with severe myocarditis is highly effective. (False)	111	(57.8)					
		Average		(60.8)	(60.0)		(18.1)		(5.1)

Abbreviation: ICI, immune checkpoint inhibitors; irAE, immune-related adverse event.
[a] ICI-specific knowledge.
[b] General knowledge required for cancer nursing.

Table 3. Association Between Basic Statistics, Personal and Environmental Attributes (Q1), and Knowledge Test Scores (Q3)

***N*=192**

Attributes (Q1)				Knowledge Test Scores (Q3)				
		n	***(%)***	***M***	***SD***	***Mdn***	***p-value***	
4. Current outpatient unit	Respiratory	2	(1.0)	27	(5.657)	27	.035	[a]
	Gastroenterology	3	(1.6)	19	(1.000)	19		
	Head and neck	1	(0.5)	26	.	26		
	Chemotherapy room/ Infusion center	168	(87.5)	26.58	(5.427)	27		
	Others	18	(9.4)	23.78	(5.429)	23		
14. Participation in irAE management training								
	Yes	60	(31.3)	28.5	(4.806)	29	.000	[b]
	No	132	(68.8)	25.15	(5.467)	25.5		
15. No. of patients receiving ICI involved to date								
	1–10	26	(13.5)	23.19	(5.852)	23.5	.003	[a]
	11–20	19	(9.9)	24.47	(4.982)	24		
	21 and more	147	(76.6)	26.95	(5.275)	28		
16. No. of predictable irAEs to date	Yes	111	(57.8)	27.23	(5.262)	28	.001	[b]
	No	81	(42.2)	24.79	(5.497)	25		
17. No. of unpredictable irAEs to date	Yes	116	(60.4)	27.24	(5.426)	28	.000	[b]
	No	76	(39.6)	24.61	(5.210)	24		
18. No. of free self-study opportunities/media	0	11	(5.7)	24.18	(3.188)	24	.000	[a]
	1	37	(19.3)	23.32	(5.503)	24		
	2	38	(19.8)	24.08	(5.957)	24		
	3	48	(25.0)	27.88	(4.671)	28		
	4	33	(17.2)	27.12	(4.910)	28		
	5 and more	25	(13.0)	30.12	(3.930)	30		
19. No. of paid self-study opportunities/media	0	72	(37.5)	25.74	(5.960)	26	.005	[a]
	1	58	(30.2)	25.1	(4.887)	24.5		
	2	44	(22.9)	26.95	(5.545)	28		
	3 and more	18	(9.4)	29.72	(3.444)	30		
24. Questionnaire for ICI use or not	Yes	98	(51.0)	26.94	(5.845)	28	.027	[b]
	No	94	(49.0)	25.43	(4.991)	25.5		
25. No. of tools to confirm irAEs	Yes	150	(78.13)				.013	[b]
	No	42	(21.9)	24.57	(4.435)	25		
No. of tools for those who selected "Yes"	1	120	(62.5)	25.97	(5.783)	26		
	2	28	(14.6)	29.18	(4.234)	30		
	3	2	(1.0)	32.5	(4.950)	32.5		
26. Availability of patient education tools	Yes	169	(88.0)				.000	[b]
	No	23	(12.0)	21.61	(3.513)	21		
No. of tools for those who selected "Yes"	1	133	(69.3)	26.34	(5.496)	27		
	2	32	(16.7)	27.91	(4.468)	27		
	3	4	(2.1)	34.25	(2.754)	34.5		

Abbreviation: ICI, immune checkpoint inhibitors; irAE, immune-related adverse event; M, sample mean; Mdn, median; SD, standard deviation

[a] Kruskal–Wallis test.

[b] Mann–Whitney U test with two groups: presence and absence.

Table 4. Association Between Basic Statistics of irAE Awareness (Q2) and Knowledge Test Scores (Q3) ***N=192***

irAE Awareness (Q2)		**Knowledge Test Scores (Q3)**				
	***n*（%）**	***M***	***SD***	***Mdn***	***p-value*** [a]	***adjusted p-value*** [b]
1．I approach the patient myself to check for irAEs					.000	
Disagree	9（4.70）	20.89	（4.014）	20		
Neither	39（20.30）	24.38	（5.107）	25		
Agree	144（75.00）	27.02	（5.381）	28		
Disagree vs. Agree					.001	.003
Disagree vs. Neither					.097	.292
Neither vs. Agree					.004	.012
2. I think that patient education on the purpose behind prevention and coping behaviors is important for early detection of irAEs.					.003	
Disagree	3（1.60）	17	（2.646）	16		
Neither	12（6.30）	22.92	（4.481）	23		
Agree	177（92.20）	26.58	（5.382）	27		
Disagree vs. Neither					.192	.577
Disagree vs. Agree					.008	.025
Neither vs. Agree					.020	.061
3. I think that patient education on methods of prevention and coping is important for the early detection of irAEs.					.047	
Disagree	3（1.60）	20.33	（5.508）	20		
Neither	13（6.80）	24.23	（4.086）	25		
Agree	176（91.70）	26.44	（5.511）	27		
Disagree vs. Neither					.404	1.000
Disagree vs. Agree					.073	.220
Neither vs. Agree					.077	.232
4. I think that early detection of irAEs is the responsibility of physicians.					.958	
Disagree	49（25.50）	26	（6.608）	26		
Neither	81（42.20）	26.09	（5.080）	27		
Agree	62（32.30）	26.5	（5.076）	26.5		
5. For early detection and treatment of irAEs, I think that it is important to improve our knowledge of the antitumor effects and adverse events associated with the drugs administered to each patient.					.012	
Disagree	1（0.50）	15	.	15		
Neither	6（3.10）	21.17	（2.563）	21		
Agree	185（96.40）	26.42	（5.428）	27		
Disagree vs. Neither					.556	1.000
Disagree vs. Agree					.095	.286
Neither vs. Agree					.012	.037
6. For early detection and treatment of irAEs, I think that it is important to improve our knowledge about the onset time of adverse events for the drugs administered.					.082	
Disagree	2（1.00）	24.5	（13.435）	24.5		
Neither	10（5.20）	22.3	（5.229）	21		
Agree	180（93.80）	26.43	（5.362）	27		
7. Plan to learn about irAEs.					.000	
Already learning (more than 6 months)	68（35.40）	29.07	（3.952）	30		
Already learning (less than 6 months)	50（26.00）	26.16	（6.011）	27		
Intend to learn soon (generally within 1 month) or have started little by little	18（9.40）	24.44	（7.221）	26.5		
Intend to learn (generally within 6 months)	45（23.40）	23.51	（3.992）	23		
Do not intend to learn	11（5.70）	22.45	（4.886）	24		

Abbreviation: irAE, immune-related adverse event; M, sample mean; Mdn, median; SD, standard deviation.
[a] Kruskal–Wallis test. $p<.05$.
[b] Bonferroni correction adjusts the value of significance probability for multiple tests.

Table 5. Free comment description of the impetus for future study by 23 of the 74 respondents who are not yet learning at present n=23

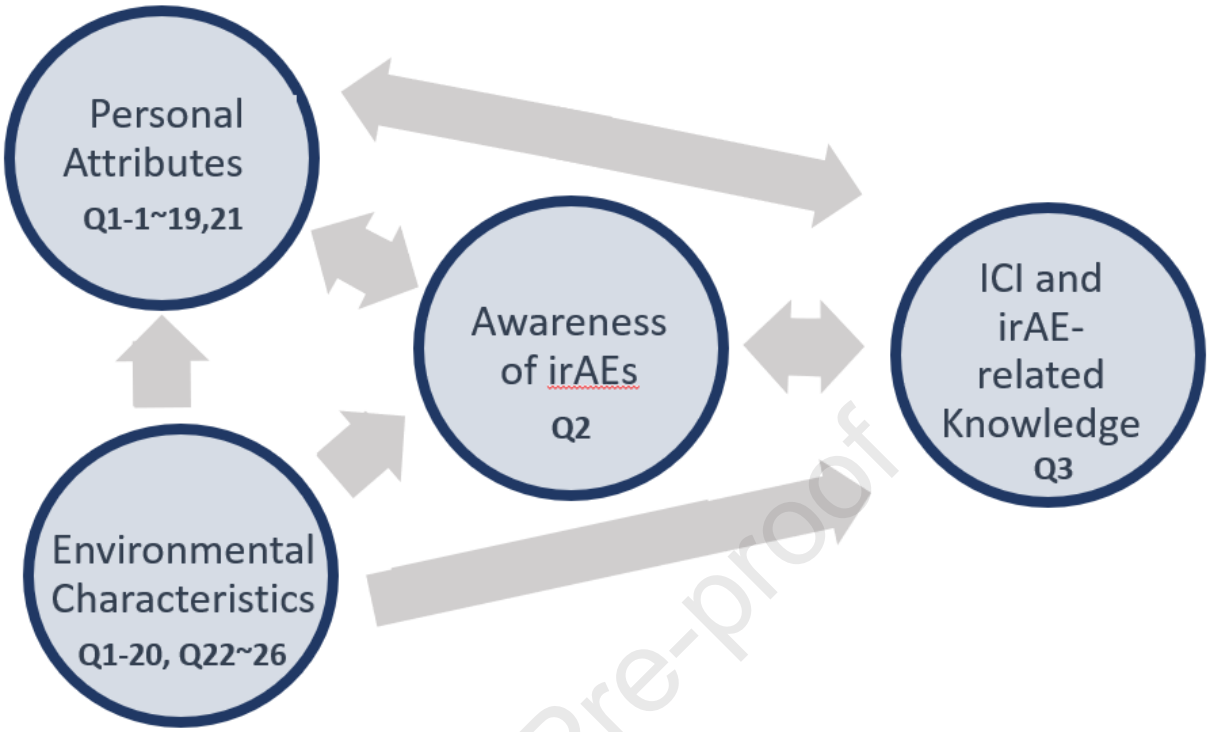
Category	Comment	n	(%)
Training Opportunity	Seminar	4	(17.4)
	Internal Seminar	2	(8.7)
Facing irAEs	irAEs	4	(17.4)
Schedule	I have a chance to start, but I am having a hard time finding the time to learn.	1	(4.3)
	There are training sessions and other events held in the hospital, but I have never been able to attend them because they are during work hours. I would like to participate and learn if there are workshops outside of work hours.	1	(4.3)
	If I have time, physical and mental capacity	1	(4.3)
	I would like to participate if my schedule allows me to attend.	1	(4.3)
Environment	Environment and content for easy participation	1	(4.3)
	Support from the facility	1	(4.3)
	When I return to work in the outpatient chemotherapy unit.	1	(4.3)
	If I have sources or the tools	1	(4.3)
	I would like to learn if there are online materials available	1	(4.3)
Others	If I have the chance to learn, I will.	1	(4.3)
	I feel the need.	1	(4.3)
	If the number of patients increases	1	(4.3)
	Hold study sessions and obtain knowledge from books and other sources if I have problems of my own.	1	(4.3)

Table 6. Multiple Regression Analysis of the Effect of Personal and Environmental Attributes (Q1) and Awareness (Q2) on ICI and irAE Knowledge Test Scores (Q3)

***N*=192**

		irAE Knowledge Test Scores (Q3)				
		Unstandardized Coefficient		Standardized Coefficient		Statistic of Collinearity
		Coefficient	Standard Errors	β	*p*	*VIF*
	(Constant)	19.717	5.644		.001	
Attribute question (Q1)	9. Qualifications held	1.657	1.090	.145	.13	2.185
	13. Membership in academic societies	.278	1.022	.024	.786	1.933
	14. Participation in irAE management training	.811	.919	.069	.379	1.458
	18. Free self-study	-1.036	1.630	-.044	.526	1.154
	25. Availability of irAE confirmation tool	.499	.953	.038	.601	1.247
	26. Availability of patient education tools	1.270	1.469	.074	.388	1.759
Awareness question (Q2)	1. I approach the patient myself to check for irAEs.	.583	.805	.059	.47	1.577
	2. I think that patient education on the purpose of prevention and coping behavior is important for early detection of irAEs.	1.195	1.453	.075	.412	1.973
	5. For early detection and treatment of irAEs, I think that it is important to improve our knowledge on the antitumor effects and adverse events associated with the drugs administered to each patient.	.787	2.150	.032	.715	1.871
	7. Plan to learn about irAEs	-.998	.343	-.242	.004	1.66

Abbreviation: irAE, immune-related adverse event; VIF, variance inflation factor.
ANOVA $p<.01$. R, .497; R^2, .247; Adjusted R^2, .205.



This conceptual diagram was originally schematized by the author. Knowledge of ICI and irAE is associated with personal attributes and environmental characteristics. Awareness of irAE is associated with personal attributes, environmental characteristics and knowledge of ICI and irAE. Personal attributes are associated with environmental characteristics.

Figure. Conceptual diagram of ICI and irAE knowledge, attributes, and awareness of irAEs