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Registry study of immune-related adverse events using electronic patient-reported outcome in patients with cancer receiving immune checkpoint inhibitors: protocol for a multicentre cohort study

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ABSTRACT

Introduction The use of immune checkpoint inhibitors (ICIs) is rapidly expanding in cancer treatment. ICIs have a unique safety profile, characterised by immune-related adverse events (irAEs). The safety profile of ICIs lacks patient experience and perspectives. This study primarily aims to obtain a database for descriptive research on the status of irAEs using the Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) in patients with gastrointestinal cancer, lung cancer and malignant pleural mesothelioma treated with regimens containing ICIs.

Methods and analysis This is an ongoing, multicentre, observational study in Japan. Eligible patients must be at least 20 years old and have been diagnosed with lung cancer, malignant pleural mesothelioma or gastrointestinal cancer and plan to use ICIs. Participants will install the electronic PRO (ePRO) application and report adverse events via ePRO using PRO-CTCAE once weekly for up to 48 weeks. A registry will be established using background information obtained from medical records. The sample size is determined by 1 year projection without using statistical methods. Statistical analyses will include point estimates and 95% CIs for the incidence of each adverse event by cancer type and regimen at each time point.

Ethics and dissemination This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, and the revised Personal Information Protection Law. The study protocol was approved by the Ethics Committee (approval ID T2021-0180) of Tokyo Medical University Hospital on 15 October 2021.

Registration details The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 have been enrolled, and the enrolment is scheduled to end on 30 June 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Insufficient information on symptom-related adverse events of regimens containing immune checkpoint inhibitors can be clarified.
⇒ Multiple insights into adverse event monitoring using Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) via electronic PRO, which can collect adverse events in real-time without patient visits in Japanese clinical practice settings, can be provided.
⇒ The selected items of PRO-CTCAE in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by a board-certified oncology pharmacy specialists and through patient public involvement.
⇒ A limitation of this study is that patients cannot be evaluated for PRO-CTCAE items not selected by the investigator at the time of planning. Not all patient-reported safety profiles are available.

Trial registration number UMIN000046418

INTRODUCTION

In 2017, the number of malignant tumour (cancer) patients and deaths worldwide were 24.5 million and 9.6 million, respectively.[1] The number of cancer patients in Japan was 775 601 in 2009.[2] Cancer treatment centres on surgery, drug therapy and radiation therapy. Recently, immunotherapy has attracted attention, and insurance coverage for immune checkpoint inhibitors (ICIs) is rapidly expanding. The following cancer types are currently covered by insurance in Japan: non-small cell lung cancer, small cell

lung cancer, malignant pleural mesothelioma, oesophageal cancer, gastric cancer, colorectal cancer, hepatocellular cancer, head and neck cancer, breast cancer, cervical cancer, uterine cancer, urothelial cancer, renal cancer, melanoma, solid tumours with high microsatellite instability-high, tumour mutational burden-high and Hodgkin's lymphoma. Among the cancers for which ICIs are indicated, in which respiratory and gastrointestinal cancers are the most common, 103 715 cases were lung cancer, 122 632 gastric cancer, 116 342 colorectal cancer, 48 003 liver cancer and 20 787 oesophageal cancer in 2009 in Japan.[2]

Adverse events in ICI treatment differ from those of conventional cytotoxic anticancer and molecular-targeted drugs in that they may present with specific autoimmune-like immune-related adverse events (irAEs).[3] Although irAEs are relatively common in the skin, gastrointestinal tract, liver, lung and endocrine organs, they can theoretically occur anywhere in the body.[4] IrAEs can occur at any time after the start and even after the completion of ICI administration.[5] Ipilimumab is reported to cause more skin irAEs after 2–3 weeks, gastrointestinal and hepatic after 6–7 weeks and endocrinal after 9 weeks.[6] In contrast, nivolumab is reported to cause more skin irAEs after 5 weeks; gastrointestinal, hepatic and pulmonary after 7–8 weeks, endocrinal after 10 weeks and renal after 15 weeks.[7] However, most irAEs were reported to occur within 6 months of prolonged treatment with nivolumab and were not cumulative.[8] Although careful monitoring is recommended after ICI administration, there is no settled opinion on the monitoring period. IrAEs should be monitored by a physician or a physician's assistant. The response varies by organ, but as a general rule, the administration should be postponed or interrupted when ≥grade 2 is reached; systemic corticosteroids should be considered. After starting treatment with steroids, it is recommended that they be tapered off over several weeks while checking for irAE recurrence and subsequently discontinued or adjusted to a low-maintenance dose.[9 10]

Patient-reported outcome (PRO) is defined as 'an evaluation method in which patients judge their symptoms and quality of life; the results are obtained without any intervention from doctors or other parties' by the Food and Drug Administration.[11] In recent years, adverse event assessment using PROs has gained prominence in oncology. Basch *et al*[12] reported that adverse event assessments in providers and patients are inconsistent, with a tendency for providers to underestimate them. This problem led to the development of a PRO version of the Common Terminology Criteria for Adverse Events (CTCAE), PRO-CTCAE, in 2008. In a randomised controlled trial, a comparison of the proactive approach with PRO-CTCAE using electronic PRO (ePRO) for adverse events with a conventional adverse event evaluation showed a significant difference in health-related quality of life and overall survival.[13] This study has attracted attention as a trial that will change clinical practice. The results have led to the use of PRO-CTCAE in many countries, including Japan.

Early detection and monitoring of irAEs are important, and PROs are useful.[14] However, Tolstrup *et al*[15] noted that the procedure for selecting PRO-CTCAE items in patients receiving immunotherapy is not well established. They reported a method for selecting PRO-CTCAE questions for patients with malignant melanoma receiving immunotherapy. Studies of PRO-CTCAE in ICI-using patients have been reported in malignant melanoma and non-small cell lung cancer.[16 17] Based on these studies, the PRO-CTCAE is used as a questionnaire to evaluate irAE; however, few studies on irAE and PRO-CTCAE are available.

In Japan, pharmacists play an important role in the rapidly advancing field of cancer pharmacotherapy. Particularly, with the increase in outpatient cancer treatment, there have been many reports on the importance and usefulness of outpatient consultations conducted by pharmacists. This report suggests that in addition to routine tasks such as checking laboratory values and providing medication guidance, working with physicians and nurses to conduct preconsultation and postconsultation interviews not only benefits patients but also helps to reduce the burden on medical staff and improves the quality of care.[18 19]

The present study, named RESPECT (REgistry Study of immune-related adverse events using electronic Patient-reported outcome in patiEnts with cancer receiving immune CheckpoinT inhibitors) study, aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. In addition, it aims to determine the rate of symptom-related adverse events at each time point in the setting in which ePRO adverse event monitoring is performed.

METHODS AND ANALYSIS

Study design

This is an ongoing, multicentre, longitudinal, observational study. An observational study design is used to track the mode and course of irAEs, focusing on symptom-related adverse events. Participants will install the ePRO application and report adverse events weekly via ePRO using PRO-CTCAE. In addition, a registry will be established using background information obtained from medical records; ancillary studies will be conducted on the proportion of adverse event reporting by ePRO and those associated with ICIs.

Patient and public involvement

The following two patient groups were asked to cooperate in participation: Non-Profit Organization Lung Cancer Patients Association One Step and General Incorporated Association Esophageal Cancer Survivor's Sharing. The research plan will include the advice given on PRO-CTCAE item selection, number of questions and survey frequency. Advice will also be obtained at each stage of the process leading up to the publication of the results.

Table 1 Study timeline (summary)

Week		0	12	24	36	48
Eligibility verification	eCRF	O				
Background						
Participant background	eCRF	O				
Psychosocial background	ePRO	●				
ECOG PS	eCRF	O				
Adverse events						
PRO-CTCAE	ePRO	●	●	●	●	●
CTCAE v5.0-JCOG	eCRF	→	→	→	→	
Laboratory data	eCRF	→	→	→	→	
Record of the time of the visit	eCRF	→	→	→	→	
Records at the time of ePRO confirmation	eCRF	→	→	→	→	
Satisfaction (CTSQ)	ePRO			●		●
A questionnaire on ePRO use	ePRO		●			
irAE (suspected/confirmed)		→	→	→	→	

O Medical professionals valuation; ● Participant assessment.
CTSQ, Cancer Therapy Satisfaction Questionnaire; ECOG PS, Eastern Collaborative Oncology Group Performance Status; eCRF, electronic case report form; (e)PRO, (electronic) patient-reported outcome; irAE, immune-related adverse event; JCOG, Japan Clinical Oncology Group; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Event.

Study setting, participants and recruitment

Recruitment is being performed at nine hospitals in Japan. The inclusion criterion is the diagnosis of lung cancer, malignant pleural mesothelioma or gastrointestinal cancer in patients who plan to use an ICI and give their written consent to participate in the study, over 20 years old and with Eastern Collaborative Oncology Group Performance Status of 0–3. Patients who do not have an ePRO-eligible device, have a severe psychiatric illness or cognitive dysfunction that affects filling out the survey form or those with a native language that is not Japanese are excluded. The study pharmacist will invite eligible patients to participate in the study at each site. After starting treatment, participants will complete weekly ePROs, adverse events monitoring questionnaires at week 12, and treatment satisfaction questionnaires at weeks 24 and 48. Observation shall be discontinued in the following cases: (1) if the participant requests to discontinue the adverse event evaluation using ePRO, (2) when follow-up is no longer possible due to hospital transfer, (3) death during follow-up, (4) if consent is withdrawn and (5) loss to follow-up.

Outcome measures

Table 1 shows the study schedule. We will use the PRO-CTCAE and the CTCAE v5.0 to assess adverse events. In addition, we will use Cancer Therapy Satisfaction Questionnaire (CTSQ) to assess treatment satisfaction.

Adverse events

Adverse events will be assessed using CTCAE v5.0, translated by the Japan Clinical Oncology Group as Clinician-Reported Outcome (ClinRO), and PRO-CTCAE as PRO. Since its development as a common toxicity criterion in 1984, the CTCAE has been the gold standard as ClinRO for adverse event assessment and is widely used in clinical research, particularly in the field of oncology. The CTCAE v5.0 will be recorded from the medical record each time they are assessed; items corresponding to PRO-CTCAE will be mandatory. Meanwhile, the PRO-CTCAE, developed by the National Cancer Institute in 2008, consists of 80 items from the CTCAE version 4, extracting 78 symptoms that can be subjectively assessed by the patients and has been reworded to make them easier for patients to answer. Each item is assessed using one or more attributes, including presence/absence, frequency, severity and/or interference with usual or daily activities. The original version has been evaluated for validity and reliability by Dueck *et al*.[20] The Japanese version of PRO-CTCAE has been validated for linguistic and psychometric validity by Miyaji *et al*[21] and Kawaguchi *et al*,[22] respectively.

Treatment satisfaction

The CTSQ is a 16-item questionnaire developed by Pfizer to measure treatment satisfaction specifically with cancer treatment. It has three subscales, 'Expectations of Treatment', 'Feelings about Side Effects' and 'Satisfaction with Therapy', which are scored from 0 to 100. Higher scores indicate higher satisfaction. This questionnaire has been validated by Abetz *et al*.[23]

Sample size determination

The sample size was not calculated based on a statistical perspective. Considering the annual number of patients treated with ICIs at each site and the proportion of smartphone or tablet ownership for ePRO, and obtaining consent, a target enrolment number of at least 260 patients per year was set.

Data collection and timeline

The study pharmacist will perform web registration for the participants' data using the electronic data capture (EDC) system, Viedoc 4 (Viedoc Technologies, Sweden). Participants will respond to the PROs using 3H P-Guardian (3H Clinical Trial Inc., Japan), an ePRO application, on their own device (smartphone or tablet) at 49 time points: at baseline and weeks 1–48 after initiating ICI therapy. The oncologist and/or study pharmacist will explain the details of this research to the patient. After obtaining patient consent, data on psychosocial background and PRO-CTCAE will be collected from the participant's electronic device. Data on demographics, medical history and CTCAE v5.0- JCOG scores will be collected and entered into EDC and linked to baseline PRO data. The study pharmacist will review ePRO data within the scope of their routine daily practice and, based on this information, share information with physicians and nurses, and contact and respond to participants, but there are no restrictions or interventions since this is for research study purposes. After the study pharmacist has reviewed the ePRO data, they will record in the EDC whether they have contacted the physician, nurse or patient, and if so, the details of that action. They will also be asked to record treatment satisfaction at weeks 24 and 48. Adverse event assessment using CTCAE and PRO-CTCAE will continue after treatment with ICIs is discontinued. The study timeline is shown in table 1.

Data monitoring

The data centre is located at the Tohoku Graduate School of Medicine (Miyagi Prefecture, Japan). To protect participants' privacy, no personally identifiable information will be entered into the EDC. Data management and central data monitoring will be performed using the EDC. Establishment of a data monitoring committee and auditing are not planned for this study. Following the data entry of this study, the fixed data will be exported and deleted from the EDC and will be stored in the research office in electronic media for at least 10 years after the principal publication.

Harm

This is a non-interventional, non-invasive, observational study. Therefore, the burden on the participants is minimal. Participant contributions for time spent filling out questionnaires, installing applications and communication costs for data transmission will be explained in writing and verbally in the consent explanation. Consent will be fully explained before enrolment, and participants can withdraw even while the questionnaire is being filled out.

Statistical analysis

The primary purpose is to obtain a database for descriptive research on the actual status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. Furthermore, we aim to determine the incidence of symptom-related adverse events at each time point in an environment where ePRO-based adverse event monitoring is conducted in daily practice. Point estimates and 95% CIs of the incidence of each adverse event at each time point by cancer type and regimen will be estimated. The treatment of missing values will not be specified in advance. In addition, we will examine the association between symptom-related adverse events and the extent of pharmacist actions and summarise the ePRO completion rate using descriptive statistics as the reality of pharmacist actions for PRO-CTCAE.

ETHICS AND DISSEMINATION

Research ethical approval

This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, and the revised Personal Information Protection Law. The protocol was approved by the Ethics Committee of Tokyo Medical University Hospital (approval ID T2021-0180) on 15 October 2021. The version of the protocol became 1.1 in March 2022. The protocol has been reviewed by the Institutional Review Boards of the following research centres: Juntendo University Nerima Hospital, JR Tokyo General Hospital, Nippon Medical School Hospital, Kyorin University Hospital, Teine Keijinkai Hospital, Nihon University Itabashi Hospital, University of Miyazaki Hospital and Japanese Red Cross Tokushima Hospital.

Consent

The study pharmacist and/or the oncologist will give the patients an informed consent form and explain the details of the study before enrolment. The participant's request to withdraw consent during or after the study will be accepted without any disadvantage.

Access to data

The study pharmacist and/or the oncologist may use the EDC to review only case data collected at their site. In addition, only the data manager at the data centre has access to the case data entered from each research site through the EDC.

Confidentiality

Three types of personal information will be used in this study: medical record number, date of birth and initials, which are the minimum required for identification and inquiry of the participant. In addition, the participant's medical history and social background, which fall under the category of personal information requiring special consideration, will be collected.

The date of birth will be collected in EDC for age calculation. Participant IDs and initials will be used only in the correspondence table for each institution; this correspondence table will not be provided to anyone other than the respective institutions. Sensitive personal information will be collected in the EDC for use as the study's participant background.

The following measures will be taken to minimise the risk of information leakage when using personal information in this study. First, all data obtained will be used only for the stated purpose. EDC and ePRO systems that comply with the respective laws and regulations will be used. Second, each research institute will create its correspondence table, which will not be shared with other third-party institutions. Third, results will be analysed and reported in a non-personally identifiable format. Fourth, in other respects, the Declaration of Helsinki, the Act on the Protection of Personal Information, and the 'Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects' will be followed.

Dissemination policy

The results of this study will be presented at major domestic and international conferences and published in English.

DISCUSSION

This study aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events. It is the first multicentre collaborative study in Japan. The profile of adverse events associated with ICIs differs from that of conventional cancer drugs. Their use has diversified from monotherapy to combination with cytotoxic regimens; management methods are not yet established. Furthermore, few studies presently use PRO-CTCAE to evaluate irAEs with ICIs. Therefore, this study will provide information on symptom-related adverse events for ICI-containing regimens in Japan, which is not fully available during the clinical trials in which adverse events were assessed only by ClinRO.

This study's database will be used to estimate the cumulative incidence of symptom-related adverse events at 3, 6, 9 and 12 months, with 2 and 3 of the PRO-CTCAE response options (from none to 0, 1, 2, 3 and 4) as onset events by carcinoma and regimen. In addition, we are considering estimating the duration of each symptom-related adverse event by defining the worsening of an adverse event from baseline as an emergence event and the duration from the emergence of the adverse event to the return to baseline as the duration of a symptom-related adverse event. As mentioned earlier, there are still many unknowns regarding the occurrence of irAEs; this study's database may provide information on trends in the occurrence of irAEs by carcinoma and regimen. We are also considering summarising the records of ePRO confirmations with descriptive statistics and examining the association between symptom-related adverse events and the degree of pharmacist action (response options) as the reality of pharmacist action for PRO-CTCAE. This item could be more clinically relevant, leading to early detection and treatment of irAEs through pharmacist action using the PRO-CTCAE. This could shorten the duration of treatment for irAEs, avoid serious events and allow cancer treatment progression, demonstrating the pharmacist's professional ability and providing valuable feedback to patients and the medical community.

The study protocol has some limitations. First, the study is a hypothetical, unconventional, observational study, and it does not include patients with all cancer types for which ICIs can be administered. Additionally, the number of patients was not determined by statistical methods but rather based on the number of patients at participating sites. Therefore, there are limitations with respect to generalisability. Second, the items of symptom-related adverse events in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by four oncology pharmacists. Therefore, it is impossible to collect information on the occurrence of other symptoms. Third, participants with cognitive impairments or psychiatric disorders and those unable to operate a smartphone or tablet are excluded from participation in this study. Most of the excluded patients are likely to be older adults. Patients with cancer in real-world practice are often older adults; age differences may be a barrier between the study and real-world practice.

The RESPECT trial may provide critical information for future treatment with ICIs in clinical practice by providing information on symptom-related adverse events that have not been adequately obtained during the clinical trials conducted before approval. In fact, the adverse event assessments from our registry will not only provide the 'worst grade during time period' used in general cancer clinical trials but also provide cumulative incidence rates and changes over time by ICIs, their regimens or by cancer type, based on temporal changes such as onset and resolution of adverse event ratings.

Study status

The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 participants have been enrolled. Enrolment is scheduled to end on 30 June 2023. The research is to be conducted from 15 October 2021 to 31 March 2028.

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Contributors AY contributed to the study conception and is the principal investigator. KA, TH, AT, DH, TK, and TY participated in the design of the study. TK and TY played a primary role in designing the data management approach. TK and TY played a primary role in designing statistical analysis. Data analysis and interpretation will be conducted by TM, TK and TY. AT, TH, KA, HU, SK, TH, DH, Yousuke Kawahara, Yuki Kumihashi, TC and TW have carried out recruitment and collected the data. All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

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