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ORIGINAL ARTICLE

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Evaluation of the usefulness of protocol-based pharmacist-facilitated laboratory monitoring to ensure the safety of immune checkpoint inhibitors in patients with lung cancer

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Abstract

What is known and objective: Immune checkpoint inhibitors can cause immune-related adverse events (irAEs). Improved monitoring systems for irAEs, which include laboratory tests by a qualified multidisciplinary team, might prevent patients from irAE-associated events. Kobe City Medical Center General Hospital developed protocol-based pharmacist-facilitated laboratory tests named protocol-based pharmacotherapy management (PBPM) to aid the administration of immunotherapy to patients with lung cancer. The protocol defines the laboratory test items and times at which they should be performed. It requires pharmacists to check laboratory orders initiated by physicians and enter additional test items if the orders are incomplete. We evaluated the efficacy of PBPM in irAE monitoring and compared it with those of conventional care systems.

Methods: From January 2016 to March 2018, 114 patients with lung cancer received immunotherapy, which was managed by conventional care (conventional group). From April to September 2018, 62 patients were managed by PBPM (PBPM group), among those 28 patients were transited from conventional group to PBPM group. Data on whether the laboratory tests were conducted or omitted were collected retrospectively for the conventional group and prospectively for the PBPM group.

Results: Within the conventional group, 4604 (87.6%) out of the 5253 laboratory test items were ordered by physicians. Of the remaining 649 test items, 224 (4.3%) items were added by physicians based on recommendations by pharmacists. However, of the 1581 (86.6%, from among 1826) test items that were previously ordered by physicians, only 231 (12.7%) test items were added by pharmacists. The execution rate was found to be significantly higher in the PBPM group (99.2% vs 91.9%, $P < .001$).

What is new and conclusion: PBPM-based pharmacist-facilitated laboratory monitoring systems provided higher executing rate of laboratory order to monitor irAEs during immunotherapy.

KEYWORDS
immune checkpoint inhibitor, immune-related adverse events, laboratory test, protocol-based pharmacotherapy management

1 | WHAT IS KNOWN AND OBJECTIVE

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed death-1 receptor (PD-1) through the programmed death-ligand 1 (PD-L1). ICIs have led to substantial improvements in the outcomes of patients with various types of cancer.[1-8] However, ICIs can cause immune activation in non-target tissues as well, resulting in immune-related adverse events (irAEs) among a subset of patients.[9] Although the majority of irAEs are mild and manageable when diagnosed early and treated appropriately, they require timely management with long-term steroid or endocrine replacement therapy, which could be life-threatening.[10-13] Furthermore, the time to onset of irAEs can vary, even months after the discontinuation of immunotherapy. Therefore, careful monitoring of irAEs by observing patient symptoms along with laboratory tests is essential.[10-14]

Manual ordering of laboratory tests may be overlooked by routine sequence tests. The usefulness of laboratory test order templates has been previously reported, which consist of laboratory test items in the form of computerized physician order entry systems.[15,16] This system allows physicians to improve their laboratory test order efficiency, in addition to facilitating optimized patient care. We have prepared and applied monthly templates for appropriate monitoring of irAEs, which were pre-entered into the laboratory test items to be measured, according to the tests covered by the Japanese insurance system. Despite the use of order templates, routine laboratory tests were still sometimes overlooked. Therefore, more appropriate and efficient monitoring systems, based on multidisciplinary team care, are required.

With this understanding, we established a protocol-based pharmaceutical care system (protocol-based pharmacotherapy management, PBPM),[17] which is an agreement between physicians and pharmacists to support laboratory order entry for patients with lung cancer and patients receiving immunotherapy. The protocol defines the laboratory test items and the time at which they should be performed and requires pharmacists to check the laboratory orders entered by physicians and include additional test items if the orders are incomplete. In this study, we evaluated the efficacy of using PBPM for irAE monitoring and compared it with that of conventional care.

2 | METHODS

2.1 | Patients and setting

We conducted a historical cohort study in 148 patients with non–small-cell lung cancer, who were treated with immunotherapies at the Department of Respiratory Medicine of Kobe City Medical Center General Hospital from January 2016 to September 2018. The protocol-based support for order entry by pharmacists was implemented on 1 April 2018, and a total of 114 patients were managed by conventional care (conventional group). In April 2018, PBPM was introduced (PBPM group). Of these 114 patients in conventional group, 28 patients were transited to PBPM group on April 2018, and an additional 34 patients started immunotherapy after.

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Kobe City Medical Center General Hospital (approval no. k190408). This study was registered at the UMIN Clinical Trials Registry as UMIN000031991 (http://www.umin.ac.jp/ctr/index.htm).

2.2 | Laboratory tests in conventional care versus PBPM

Prior to the implementation of the protocol (conventional group), we prepared monthly templates for laboratory tests to monitor irAEs by referring to the current guidelines,[10-12] literature[18-22] and according to the laboratory tests covered by the Japanese insurance system (Table 1). These templates were prepared on a monthly basis. As shown in Figure 1, before implementing the protocol-based support for order entry, physicians would order tests using the laboratory test templates. Until the day before each ICI infusion, pharmacists checked laboratory tests previously entered by physicians and recommended the physicians enter additional laboratory tests if those entered previously were incomplete, relative to the defined laboratory items (Table 1).

On 1 April 2018, we developed a protocol, according to PBPM, to monitor laboratory tests for immunotherapy-treated lung cancer patients with irAEs (Figure 1). We introduced the protocol in agreement with physicians and pharmacists to support laboratory order entry for patients with lung cancer receiving immunotherapy. The protocol defines both the laboratory test items and the time at which they should be performed (Table 1) and requires

TABLE 1 Components of the laboratory test order templates at the Department of Respiratory Medicine of our hospital

Timing of measurement	Laboratory test items
Baseline	Glucose, HbA_{1c}, C-peptide, free T4, free T3, TSH, TgAb, TPOAb, anti-GAD antibody, albumin, ACTH, cortisol, urine qualitative, urinary sediment, urinary NAG, urinary beta 2-microglobulin
During the 1st month after the start of immunotherapy	Glucose, free T4, free T3, TSH, urine qualitative, urinary sediment
During the 2nd month after the start of immunotherapy	Glucose, HbA_{1c}, free T4, free T3, TSH, urine qualitative, urinary sediment
During the 3rd month after the start of immunotherapy	Glucose, free T4, free T3, TSH, albumin, ACTH, cortisol, urine qualitative, urinary sediment
During the 4th month and later after the start of immunotherapy	Glucose, free T4, free T3, TSH, albumin, urine qualitative, urinary sediment
Every 3 mo	ACTH and cortisol will be added to the items during the 4th month and later after the start of immunotherapy

Abbreviations: ACTH, adrenocorticotropic hormone; GAD, glutamic acid decarboxylase; NAG, *N*-acetyl-β-D-glucosaminidase; TgAb, antithyroglobulin antibodies; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

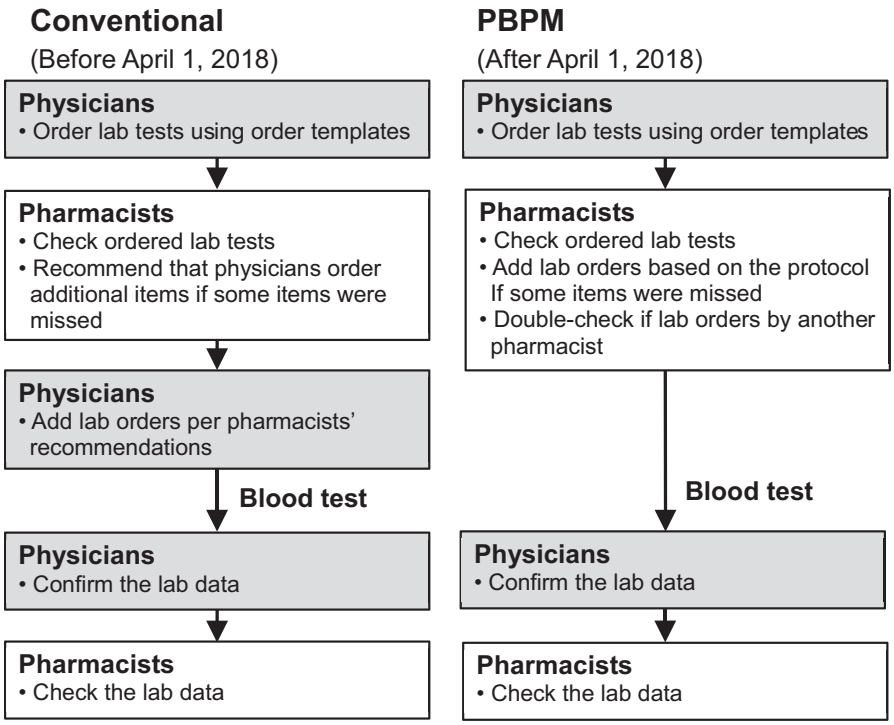

FIGURE 1 Workflow of pharmacist-supported laboratory test order entry before and after the introduction of protocol-based pharmacotherapy management. lab, laboratory; PBPM, protocol-based pharmacotherapy management

pharmacists to check laboratory orders entered by the physicians and then enter additional test items if the orders are incomplete in terms of the defined laboratory test items and timing. Pharmacists manually checked the laboratory tests ordered by the physicians. All laboratory orders added by a pharmacist were double-checked by another pharmacist. In this study, laboratory tests other than those listed in Table 1 were also allowed at a physician's discretion. In addition to the above-mentioned laboratory test items, complete blood count, serum creatinine, and liver function tests were also routinely monitored in both the conventional and PBPM groups.

2.3 | Data collection and outcomes

The primary objective was to compare the execution rates of laboratory tests before and after the introduction of PBPM to appropriately monitor irAEs. Before introducing PBPM, all data were retrospectively collected from the electronic medical record system. After introducing PBPM, data were collected prospectively. The execution rate (%) of laboratory tests was calculated as follows: [the total number of laboratory test items examined each month]/[the total number of laboratory test items that should be ordered on a monthly basis based on our internally-defined laboratory tests

(Table 1)] × 100. In cases where the defined laboratory tests were examined within a month, we considered the laboratory test to have been examined appropriately. The secondary end points included the availability of laboratory test order templates to monitor irAEs in a real-world setting and the time required for pharmacists to check and recommend to physicians that missing laboratory tests should be ordered (in the conventional group), as well as entry of additional laboratory orders in case the physicians neglected ordering appropriate laboratory tests (in the PBPM group). Our protocol stipulated that clinical pharmacists who work in the ward of the Department of Respiratory Medicine or in the ambulatory cancer centre can order laboratory tests. The mean experience in cancer chemotherapy of pharmacists who performed this PBPM was 6.6 ± 4.2 years. The time required by pharmacists was measured by analysing a group of six pharmacists with more than 6 months of experience in this practice. The mean time was measured for each entry procedure by using three representative cases of ICI treatment before and after implementation of PBPM.

2.4 | Statistical analyses

Continuous variables were expressed with median and range, while categorical variables were expressed with number and per cent. To compare the implementation rates of laboratory orders before and after implementation of PBPM, we used the chi-square test. The time required for the intervention was presented as the mean ± standard deviations and compared using the paired t-test in the same pharmacists before and after implementation of PBPM. We used JMP 13.2.1 (SAS Institute Inc) for all statistical analyses, and two-tailed *P* values < 0.05 were considered statistical significance.

3 | RESULTS

From January 2016 to September 2018, 148 patients with non–small-cell lung cancer were treated with ICIs (Table 2). Our protocol-based support for order entries by pharmacists was implemented in April 2018. As shown in Figure 2, 114 patients were managed by conventional care (the conventional group). Of these 114 patients, 28 patients received immunotherapy from 1 April 2018, with an additional 34 patients who had begun immunotherapy after April 2018 being managed by PBPM thereafter (the PBPM group). The characteristics of all the patients are summarized in Table 2. The cohort comprised 107 men and 41 women with a median age of 69 years (range: 39-92 years). A total of 116 (78.4%) patients were treated with nivolumab, following which 22 (14.9%), 9 (6.1%), and 1 (0.7%) were treated with pembrolizumab, durvalumab, and atezolizumab, respectively.

As shown in Figure 3, for the conventional group, physicians ordered 4604 (87.6%) of the 5253 laboratory test items that were meant to be ordered for monitoring irAEs by using the prepared

TABLE 2 Patient characteristics

Characteristic	Value (n = 148)
Median age (range), y	69 (39-92)
Male, n (%)	107 (72.3%)
ECOG PS, n (%)	
0-1	134 (90.5%)
2	14 (9.5%)
Histologic type, n (%)	
Adenocarcinoma	107 (73.7%)
Squamous	31 (17.5%)
Other	10 (8.8%)
Prior chemotherapy, n (%)	
0	31 (20.9%)
1	57 (38.5%)
2 or more	60 (40.5%)
Immune checkpoint inhibitor, n (%)	
Nivolumab	116 (78.4%)
Pembrolizumab	22 (14.9%)
Durvalumab	9 (6.1%)
Atezolizumab	1 (0.7%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

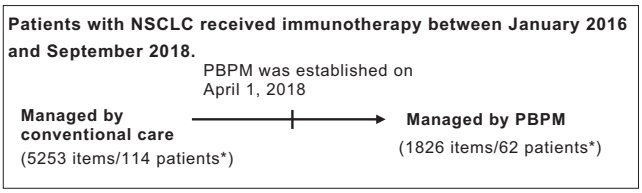

FIGURE 2 Establishment of protocol-based pharmacotherapy management. *Twenty-eight out of the 114 patients who stared immunotherapy before April 2018 continued immunotherapy after 1 April 2018. NSCLC, non–small-cell lung cancer; PBPM, protocol-based pharmacotherapy management

monthly laboratory test templates. Although pharmacists recommended that physicians should order the remaining 649 laboratory test items, only 224 (34.5%) items were ordered within an appropriate time frame. In contrast, for the PBPM group, physicians ordered 1581 (86.6%) of the 1826 laboratory test items that were meant to be ordered for monitoring irAEs. Pharmacists added 231 (12.7%) laboratory tests, and 14 (0.8%) were overlooked. As a result, the execution rate of laboratory tests was significantly higher in the PBPM group than in the conventional group (99.2% [1812/1826] vs 91.9% [4828/5253], $P < .001$). For all the laboratory test items ordered for the conventional group, the execution rate was less than 80% (Table 3). This included the cortisol level test during the 3rd (30.0% [6/20]) and 6th months (78.6% [11/14]); adrenocorticotropic hormone (ACTH) test during the 3rd (54.5% [24/44]) and 6th months (71.4% [10/14]); and urinary sediment test during the 2nd month (70.4% [19/27]). Laboratory test items that were not used every

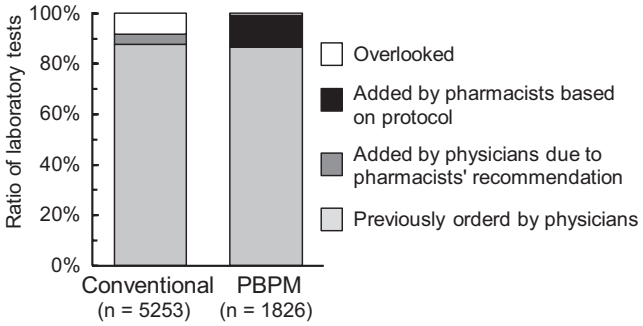

FIGURE 3 Execution rates of laboratory tests before and after the introduction of protocol-based pharmacotherapy management. The execution rates were evaluated in a total of 148 patients (114 in the conventional group and 62 in the PBPM group). PBPM, protocol-based pharmacotherapy management

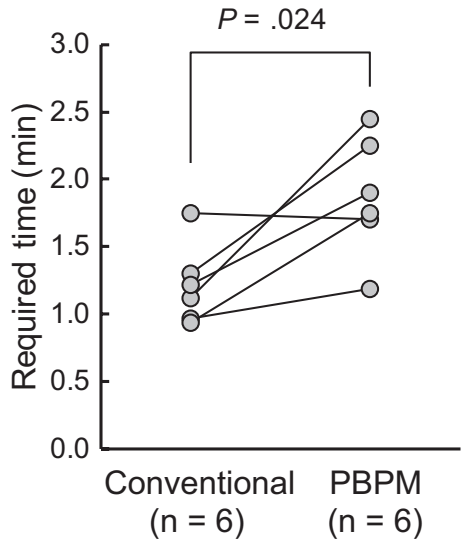

FIGURE 4 Comparison of time required by pharmacists before and after the introduction of protocol-based pharmacotherapy management. PBPM, protocol-based pharmacotherapy management

month tended to be overlooked. After the introduction of PBPM, the execution rates for all laboratory test items reached more than 80%.

The time required for interventions was measured to analyse the efficiency of the irAE-monitoring intervention by the pharmacists. This consisted of the time required for checking the order entry and implementing recommendations for the physicians to enter additional laboratory tests before introducing PBPM, and checking the order entry to enter missing items after introducing PBPM. Before introducing PBPM, the mean time required was 1.21 ± 0.30 min/course, while that after the implementation of PBPM was 1.87 ± 0.45 min/course, indicating that working hours significantly prolonged after the introduction of PBPM (P = .024; Figure 4).

4 | DISCUSSION

The majority of irAEs are mild and manageable when diagnosed early and treated appropriately; however, in some cases, they could be life-threatening.[9-13] In addition, the time to onset of irAEs can vary and they could occur even after the discontinuation of immunotherapy. Thus, a multidisciplinary team approach for careful monitoring and appropriate management of irAEs is essential. However, few studies investigating the team approach to monitoring and managing irAEs have been published.[23,24] In this study, after the introduction of PBPM for laboratory tests to monitor irAEs, the execution rates of laboratory tests significantly increased from 91.9% to 99.2%. To our knowledge, this is the first study to investigate the usefulness of pharmacist-facilitated monitoring of irAEs in cancer patients receiving immunotherapy. However, 0.8% of test items were still overlooked after the introduction of PBPM. This result also suggests that PBPM is a very useful collaborative model, but it is not perfect because it involves manual checking and ordering.

In the United States, pharmaceutical activities according to the Collaborative Drug Therapy Management (CDTM) have been expanded and legislated in 48 states (94%) in 2015.[25] In April 2010, the Japanese Ministry of Health, Labour and Welfare issued a notification to promote medical team care.[17] In that notification, the ministry encourages pharmacist involvement for appropriate and efficient support in drug selection, dosage, administration method, dosing interval and laboratory test orders. These supports would be based on protocols that have been developed and approved jointly by physicians and pharmacists. In our hospital, we established our protocol-based procedure for laboratory orders to ensure detailed monitoring of irAEs in immunotherapy-treated patients with lung cancer. Although PBPM is similar to CDTM, there are slight differences in activities involving pharmacists, which are guided by certain regulations in Japan and the United States.[18]

We also evaluated the availability of the laboratory test order templates to monitor irAEs in a real-world setting. Since the usefulness of laboratory order templates to reduce the time and effort of physicians while accurately performing test orders has been reported,[15,16] we also applied this system. The rate of laboratory tests previously entered by physicians by using laboratory test templates was 87.6% in the conventional group. After introducing protocol-based pharmacist-facilitated order entry, the rate of laboratory tests entered by physicians was 86.6%, which is almost equal to that in the conventional group. This result confirmed that preparing laboratory order templates had certain effects. Most laboratory test items with an execution rate of 80% or less are items that are not normally measured every month (cortisol and adrenocorticotropic hormone); we speculate that these lower execution rates are due to physicians copying and pasting orders they used previously.

The average time required for pharmacists in the conventional group was estimated to be 1.21 minutes. In 2018, 672 courses of ICI were administered to 82 lung cancer patients at our hospital. When multiplying the required time for checking and recommending laboratory tests for complete courses, the total working hours of pharmacists were estimated to be 13.6 hours per year (1.21/60 × 672). However, 425 (65.5%) out of the 649 recommendations for additional orders executed by pharmacists were

TABLE 3 Execution rates of the laboratory test items before and after the introduction of protocol-based pharmacotherapy management

Laboratory test items	Baseline	During the months after the start of immunotherapy					
		1st month	2nd month	3rd month	4th month	5th month	6th month
Conventional care							
ACTH	99.1%	—	—	54.5%	—	—	71.4%
Cortisol	99.1%	—	—	30.0%	—	—	78.6%
TSH	99.1%	90.2%	93.1%	88.6%	88.6%	86.7%	84.6%
Free T4	99.1%	91.3%	93.1%	88.6%	88.6%	86.7%	84.6%
Urinary sediment	99.1%	91.3%	70.4%	84.1%	82.9%	86.7%	84.6%
Others	99.0%	89.1%	87.9%	90.9%	94.2%	92.4%	89.3%
PBPM							
ACTH	100%	—	—	100%	—	—	100%
Cortisol	100%	—	—	100%	—	—	100%
TSH	100%	100%	100%	100%	100%	100%	100%
Free T4	100%	100%	100%	100%	100%	100%	100%
Urinary sediment	100%	100%	100%	100%	100%	100%	88.9%
Others	99.3%	98.8%	100%	100%	100%	96.1%	100%

Note: The execution rates in both groups were shown within first 6 mo after the start of immunotherapy.

Abbreviations: ACTH, adrenocorticotropic hormone; PBPM, protocol-based pharmacotherapy management; TSH, thyroid-stimulating hormone.

overlooked by physicians. That is, 8.7 hours per year (65.5% out of 13.6 hours) did not contribute to patient care. In contrast, the average time required for pharmacists in the PBPM group was estimated to be 1.87 minutes. When multiplying that with the time required to check for additional laboratory tests for complete courses, the working hours of pharmacists required were estimated to be 21.0 hours (1.87/60 × 672) per year. Although the working hours of the pharmacists prolonged by 7.4 hours per year in the PBPM group, the execution rate was extremely high, whereby most of the effort contributed to patient care. Although we have not investigated how much the burden on physicians has been reduced by performing PBPM, we estimate that our collaborative model could reduce the working hours of physicians by 7.21 hours per year. Taken together, our collaborative model should provide more efficient multidisciplinary team care for patients.

For appropriate ICI treatments, multidisciplinary team care is essential. Pharmacists can play important roles in managing irAEs, including education of healthcare providers and patients about potential irAEs, monitoring both clinical symptoms and laboratory tests, discussing with physicians about treatment irAEs, and teaching patients on how to use supportive care medicine for the management of irAEs.

There are several limitations in this study. First, this was a single-centre, non-randomized, observational study with retrospective evaluation of laboratory order entries in historical controls. Second, our study did not evaluate clinical outcomes, such as early detection, severity of irAEs, or survival. Third, since order entry systems are different in each hospital, the complexity for physicians to order laboratory tests may also vary depending on the hospital. In addition, laboratory test items that could be measured for the early detection of irAEs as well as the time to conduct these tests have not been established. Therefore, the effects of pharmacist-facilitated laboratory test orders for monitoring irAEs may slightly differ between hospitals. However, the results of our study indicate that protocol-based pharmacist support can markedly improve the execution rate of laboratory tests for monitoring irAEs in cancer patients receiving immunotherapy.

5 | WHAT IS NEW AND CONCLUSION

We established a PBPM-based laboratory monitoring system facilitated by pharmacists to detect irAEs in immunotherapy-treated patients with lung cancer. The use of the system significantly improved the rate of laboratory testing. The results of this study provide suggestions for more appropriate and efficient monitoring systems as part of multidisciplinary team care.

CONFLICT OF INTEREST

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