Research Article

Application of the Plan-Do-Check-Act Cycle for Managing Immune-Related Adverse Events

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Abstract: Background: Immune checkpoint inhibitors (ICIs) sometimes cause immune-related adverse events (irAEs), the timing of occurrence of which is difficult to predict. We created a system to safely manage the patients treated with ICIs who visit hospital during an emergency.

Methods: We utilized the Plan-Do-Check-Act (PDCA) cycle method to improve the quality of countermeasures for irAEs in the emergency room. First, an icon showing the patients treated with ICIs was developed for inclusion in electronic medical records. Second, ICI-specified urgent sets of clinical laboratory tests were prepared to cover the spectrum of irAEs. Third, a direct call system to either the attending physician or the chemotherapy team was established. A flow chart for managing irAEs has been prepared since September 2018. We retrospectively analyzed the electronic medical records from September 2018 to December 2020 to determine the effectiveness of the developed system.

Results: In the first cycle of PDCA, 24 patients administered ICIs were retrospectively surveyed and seven visited the emergency room. Six cases were examined according to the flow chart, whereas the other patient complaining of grade 2 diarrhea were not examined because of incomplete knowledge regarding ICIs and irAEs. As part of the "Act" step, we reminded the doctors of the flow chart and gave a lecture to the residents on how to manage irAEs. During the second and seventh cycle, no cases were observed without consulting the flow chart.

Conclusions: Quality improvement activities for the management of irAEs were conducted using the PDCA cycle methodology. Patients on ICIs are now being continuously monitored to further improve management quality.

Keywords: Immune checkpoint inhibitor, immune-related adverse event, Plan-Do-Check-Act cycle, emergency room, quality improvement, multidisciplinary team.

BACKGROUND

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and significantly prolonged the survival of patients with the specific types of cancer [1-5]. However, these inhibitors can also trigger autoimmune reactions referred to as immune-rerated adverse events (irAEs), and include skin rash, enterocolitis, pneumonitis, and endocrine disorders [6, 7].

With expansion in the approved uses of ICIs for many types of cancer, irAEs have been observed in

multiple organs during or even after the end of ICI treatment. Because general physicians as well as medical oncologists encounter patients treated with ICIs in the clinical setting, managing such patients has become common practice in the emergency room (ER).

Therefore, we aimed to improve the quality of chemotherapy concerning ICI and management of these patients during emergency visits. We utilized the Plan-Do-Check-Act (PDCA) cycle method [8, 9], which has been reported as useful one for improving quality management of infectious disease, but not in cancer medicine. So, our approach using PDCA cycle method is helpful as a model to improve not only ICI treatment but also cancer medical areas.

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METHODS

A pilot study was conducted to investigate the medical records of patients treated with ICIs who visited ER from February 2016 to December 2017. The chemotherapy team exchanged opinions with the doctors who encountered these patients. Through this survey, the following points were noted.

- # Sharing information on the administration history of ICIs during an emergency visit is crucial.
- # Detection of irAEs, particularly endocrine disorders, based on patient complaints of symptoms is difficult.
- # Residents who typically have a first approach for patients in the ER are unfamiliar with either ICI treatment or irAEs.
- # There is no consultation system regarding irAEs when the attending physician is off duty.

These problems were reviewed by the chemotherapy team, and the PDCA cycle was implemented as follows.

Plan

- An icon should be included in the electronic medical records to show which patients are currently or were previously administered ICls.
- II. ICI-specified urgent sets of clinical laboratory tests should be performed to cover the spectrum of irAEs.
- III. A direct call system should be made, starting with the attending physician or chief doctor of the same department, followed by the chemotherapy team.
- IV. This information should be disseminated to all medical staff.

Do

- We developed an icon for inclusion in electronic medical records to show which patients were treated with ICIs (Figure 1).
- II. Urgent sets of clinical laboratory tests were prepared through collaboration of the chemotherapy team and Department of Medical Safety Management (Table 1A).

- III. A flow chart of the direct call system was prepared in September 2018 (Figure 2).
- IV. We informed all medical staff of the flow chart at the doctors' office and head nurses' committee and disseminated the chart using the local network system.

Check

 These plans are assessed every 4 months by investigating the electronic medical records of patients who visited the ER.

Act

 The assessment is reviewed by the chemotherapy team. Any new or unresolved concerns are incorporated into the next cycle to improve the process.

RESULTS

The ICIs used in Nagoya Memorial Hospital are listed in Table 2. Our preliminary survey before planning the PDCA cycle revealed that 32 patients were treated with ICIs and 4 patients had emergency visits. Residents first saw these patients at the ER and then consulted with a senior doctor on duty or chief physicians. These cases were handled appropriately without incident; however, there was a request for a system tool to describe the administration history of ICIs. As a plan for the PDCA cycle, an icon showing which patients had been treated with ICIs was included in the electronic medical records in September 2018 based on the request (Figure 1). This icon is shown on the top window of the medical record, and can be immediately recognized by the medical staff. Second, ICI-specified urgent sets of clinical laboratory tests were prepared to cover the spectrum of irAEs (Table 1A). Third, the flow chart of a direct call system was prepared (Figure 2). We informed all doctors and nurses of this flow chart at the doctors' office and head nurses' committee and disseminated this information using the local network system.

In the first cycle of PDCA between September and December 2018, 24 patients were treated with ICIs and seven visited the hospital because of an emergency. The reasons for visiting the ER were infection in two cases, irAEs in two cases, disease burden in two cases, and tumor pain in one case. Six cases were evaluated according to the flow chart, whereas one case with grade 2 diarrhea was not examined at the

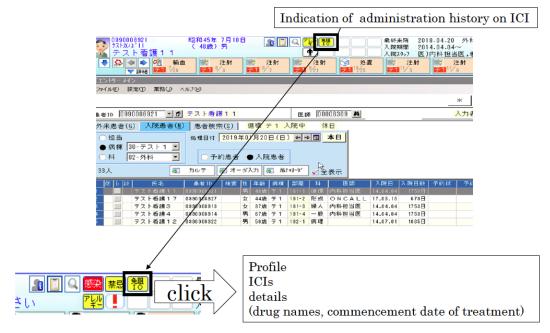


Figure 1: Electronic medical record icon showing patients treated with ICIs.

- 1. Ensure the administration history of ICIs based on the icon in the electronic records.
- 2. Carry out urgent sets of clinical examination if the patient has a symptom of irAE and consult with a senior doctor on duty.

In case of difficulty in the management of patients on ICIs,

- ① Consult the attending physician or a chief doctor in the same department
- 2 Consult doctors on the chemotherapy team (two medical oncologists) without hesitation

Figure 2: Flow chart of direct call system to manage irAEs.

emergency department because knowledge on ICIs and irAEs was incomplete. We reminded the doctors to use this flow chart at doctors' office committee again, and gave a lecture to residents who encountered patients in the emergency department on the importance of irAEs and how to manage these patients. From the second to seventh cycle of the PDCA, some patients had emergency visits in each cycle (Table 3), and all patients were appropriately handled according to the manual.

Through discussion with the multidisciplinary chemotherapy team, we applied countermeasures for earlier detection of irAEs. First, we created an irAE-specific test set in February 2018 which was performed periodically before and after starting ICI treatment

(Table **1B,C**). In the fourth cycles of PDCA (September to December 2019), the rates of ICI-specific testing were examined for each department; the rates before and after introduction of the irAE-specific test set were compared. Before initiating ICI treatment, the check rate of thyroid-stimulating hormone (TSH), free triiodothyronine (FT₃), free thyroxine (FT₄), and KrebsvonderLungen-6 (KL-6) was 92%, which was the same as before introduction of the test set (Table 4). The check rates of hemoglobin A1c (HbA1c), cortisol, and adrenocorticotropic hormone (ACTH) increased from 62% to 89%, 69% to 100%, and 46% to 100%, respectively. After initiating ICI treatment, the check rates of TSH, FT₃, and FT₄ were the same (92%), and those of KL-6, surfactant protein D (SP-D), and HbA1c improved from 54% to 65%, 46% to 54%, and 54% to

Table 1: ICI-Specific Test Set

Disease	Test item
Thyroid disease	TSH, FT3, FT4
Interstitial lung disease	KL-6, SP-D, Chest X-ray
Diabetes mellitus	HbA1c
Adrenal insufficiency, Hypophysitis	Cortisol, ACTH
Myocarditis	ECG

B. Set before starting ICI treatment.				
Disease	Test item			
Thyroid disease	TSH, FT3, FT4			
Interstitial lung disease	KL-6, SP-D, Chest X-ray			
Diabetes mellitus	HbA1c			
Adrenal insufficiency, Hypophysitis	Cortisol, ACTH			
Myocarditis	ECG			

C. Set after starting ICI treatment.					
Disease	Test item				
Thyroid disease	TSH, FT3, FT4				
Interstitial lung disease	KL-6, SP-D				
Diabetes mellitus	HbA1c				

ICI: immune checkpoint inhibitor, TSH: thyroid-stimulating hormone, FT₃: free triiodothyronine, FT₄: free thyroxin; KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D, HbA1c: hemoglobin A1c, ACTH: adrenocorticotropic hormone, ECG: electrocardiogram.

Table 2: Immune Checkpoint Inhibitors that have been used at Nagoya Memorial Hospital

Mechanism	Generic name	Cancer type	Medical department
Anti-PD-1 antibody	Nivolumab	Lung	Respiratory Medicine
		Gastric	Medical Oncology
		Lymphoma	Clinical Oncology
		Renal	Urology
	Pembrolizumab	Lung	Respiratory Medicine
		Bladder	Medical Oncology
Anti-PD-L1-antibody	Atezolizumab	Lung	Respiratory Medicine
	Durvalumab	Lung	Respiratory Medicine

Anti-PD-1 antibody: anti-programmed cell death 1 antibody. Anti-PD-L1 antibody: anti-programmed cell death-ligand 1 antibody.

62% (Table 5), but were not sufficient even after introduction of irAE-specific test set. These results indicate that doctors were generally not aware that irAEs, including endocrine disorders, can occur at any time. Therefore, continuous monitoring was initiated by

the chemotherapy team to check the implementation of the irAE-specific test. If the test set was not scheduled by doctors, the chemotherapy team reminded the attending doctors to order a test set every month. In the "Act" step of the PDCA, we gave a lecture to new

Table 3: Check of PDCA Cycle

Cycle	Durations	Patients on ICI	Emergency visit	Reasons	irAEs
1	September- December, 2018	24	7	Infection(2) irAE(2) Tumor burden(2) Tumor pain(1)	Diarrhea (grade 2) Vomiting (grade 3)
2	January-April, 2019	24	7	Infection (3) irAE (2) Tumor pain (1) Cough (1)	Adrenal insufficiency (grade 2) Nausea (grade 1)
3	May-August, 2019	25	5	Infection(2) irAE(1) Tumor burden(1) Underlying disease burden(1)	Acute renal failure (grade 3)
4	September- December, 2019	25	5	irAE (1) Tumor burden (3) Tumor pain (1)	Skin eruption (grade 2)
5	January-April, 2020	26	3	Tumor burden (1) Underlying disease burden (2)	
6	May-August, 2020	27	6	Infection (5) Adrenal insufficing irAE (1) (grade 3)	
7	September- December, 2020	26	6	Infection (1) irAE (1) Tumor burden (2) Underlying disease burden (2)	Diarrhea (grade 1)

irAEs: immune-related adverse events.

Table 4: Comparison of Check Rates before Starting ICI Treatment between Pre- and Post-Introduced ICI-Specific Test

Test item		Total (%)	Respiratory Medicine (%)	Urology (%)	Medical Oncology (%)	
TSH	pre	92	100	100	67	
	post	92	94	100	100	
FT3	pre	92	100	100	67	
	post	92	94	100	100	
FT4	pre	92	100	100	67	
	post	92	94	100	100	
KL-6	pre	92	100	75	100	
	post	92	100	60	100	
SP-D	pre	77	83	50	100	
	post	73	60	100	100	
HbA1c	pre	62	50	67	67	
	post	89	89	60	100	
Cortisol	pre	69	100	75	0	
	post	100	100	100	100	
ACTH	pre	46	100	0	33	
	post	100	100	100	100	
Chest X-ray	pre	100	100	100	100	
	post	100	100	100	100	
ECG	pre	69	83	25	100	
	post	92	89	100	100	

TSH: thyroid-stimulating hormone, FT_3 : free triiodothyronine, FT_4 : free thyroxin; KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D, HbA1c: hemoglobin A1c, ACTH: adrenocorticotropic hormone, ECG: electrocardiogram.

Table 5: Comparison of Check Rates after Starting ICI Treatment between Pre- and Post-Introduced ICI-Specific Test Set

Test item		Total (%)	Respiratory Medicine (%)	Urology (%)	Medical Oncology (%)
TSH	pre	92	100 100		67
	post	92	100	80	100
FT3	pre	92	100	100	67
	post	92	100	80	100
FT4	pre	92	100	100	67
	post	92	100	80	100
KL-6	pre	54	67	25	100
	post	65	50	80	100
SP-D	pre	46	67	0	67
	post	54	56	80	100
HbA1c	pre	54	17	75	67
	post	62	56	100	100

TSH: thyroid-stimulating hormone, FT₃: free triiodothyronine, FT₄: free thyroxin; KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D, HbA1c: hemoglobin A1c, ACTH: adrenocorticotropic hormone.

Table 6: Immune-Rerated Adverse Events in Outpatient Setting from September 2018 to December 2020

irAEs	Grade				
	1	2	3	4	
Nausea	2				
Vomiting	2		1		
Anorexia	2	2	1		
Diarrhea	2	3			
Oral mucositis		2			
Rash	2	4			
Hypothyroidism		6			
Hyperthyroidism	2				
Adrenal insufficiency		3	1		
Diabetes mellitus	1		1		
Liver dysfunction	4				
Acute renal failure		1	1		
Pneumonitis		1		1	
Panniculitis		1			
Ventricular arrhythmia		1			

residents and continuous monitoring was performed by the chemotherapy team.

In the fifth cycle (January to April 2020), 26 patients were administered ICIs and 3 patients visited the hospital for an emergency. The reasons for visiting the ER were tumor burden in one case and underlying

disease burden in two cases. The implementation rates of irAE-specific testing gradually increased to 89% for TSH, FT₃, and FT₄; 78% for KL-6 and SP-D; and 67% for HbA1c. The doctors intentionally did not order these tests each month because health insurance may not cover the cost of ICI-specific testing once per month. Accordingly, we encouraged the physicians to

implement ICI-specific testing every other month. In addition, based on academic society reports [10-12], cortisol, ACTH, and general urine tests were added to the follow-up test set.

In the sixth cycle (n=27), six patients visited the ER for infection in five cases and an irAE in one case. One patient with an irAE had grade 3 adrenal insufficiency and was treated according to the manual, leading to hospitalization. In the seventh cycle (n=26), six patients visited the ER for infection in one case, irAE (grade 1 diarrhea) in one case, tumor burden in 2 cases, and underlying disease burden in 2 cases.

In the second to seven cycle, all cases were handled according to the manual, implementing the action to inform doctors and residents suitably of the flowchart and management of irAE.

From September 2018 to December 2020, ICIs were administered to 46 patients with cancer in outpatient settings. Among them, 28 patients developed irAEs as shown in Table 6. These irAEs were diagnosed at either periodical consultation or emergency visit. Among them, 82% (23 patients) were mild to moderate irAEs, but 18% (5 patients), severe more than grade 3.

DISCUSSION

We aimed to improve the quality of treatment with ICIs using the PDCA cycle method. Although there are several reports on using the PDCA cycle method to improve the quality management of infectious disease [8, 9], few are available in the oncology field.

Guidelines for managing irAEs are available in western countries [13, 14]. As irAEs can occur at any time, either during treatment with ICIs or even after discontinuation of treatment, the patients must be continuously and closely monitored [6, 7]. In addition, the indication for ICI therapy has been extensively expanded, increasing the number of patients being administered ICIs. Therefore, more patients treated with ICIs are expected to visit the hospital for emergencies. In our hospital, residents inexperienced in cancer medicine often have a first approach to such patients in the ER. To improve the quality irAE management, four countermeasures were planned and implemented in the first cycle of the PDCA. In analyzing the first cycle of the PDCA, we found that a patient complained of grade 2 diarrhea during visits to the ER at night, and returned home only with

symptomatic treatment but no specific examinations or consultations with a senior doctor. As this incident was mainly caused by the resident's lack of awareness of irAEs, several lectures were held to inform the residents of how to manage irAEs as the "Act" step.

In Table 6, three patients were directly admitted to our hospital because of grade 3 irAEs such as anorexia, vomit, acute renal failure and adrenal insufficiency. All patients eventually recovered from the irAEs because of the early diagnosis and treatment. Two patients with severe-grade irAEs, pneumonitis and type 1 fulminant diabetes mellitus, did not come to the ER but rather attended outpatient consultation appointments. A patient had developed grade 4 pneumonitis by the time he had been consulted on his reserved outpatient day and was hospitalized. Considering these cases, patients should be also educated on irAEs and the importance of undergoing medical examination as soon as possible before developing a severe condition. Moreover, three patients consulted their family doctors before visiting our hospital; thus, to manage patients with cancer being administered ICIs, it is important to share information and cooperate with local clinics.

CONCLUSIONS

We conducted quality improvement activities with a multidisciplinary team for managing irAEs, particularly in cases of emergency visits. Successful management of irAEs should involve early diagnosis and close monitoring of patients administered ICIs. Use of the PDCA cycle method will contribute to improving the quality and security of ICI treatment.

LIST OF ABBREVIATIONS

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

PDCA cycle = Plan-Do-Check-Act cycle

ER = emergency room

TSH = thyroid-stimulating hormone

 FT_3 = free triiodothyronine

 FT_4 = free thyroxin

KL-6 = Krebsvonder Lungen-6

HbA1c = hemoglobin A_{1c} SP-D = surfactant protein D

ACTH = adrenocorticotropic hormone

DECLARATIONS

Ethics approval and consent to participate.

The protocol of this study was approved by the ethics committee of Nagoya Memorial Hospital (approval No. 2021-007) and conducted in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable.

AUTHORS' CONTRIBUTIONS

SH, KI wrote the manuscript. SH reviewed the medical records. All authors read and approved the final manuscript.

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