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Implementation of an Adverse Drug Reaction Monitoring System Based on Risk Management Plans

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Abstract

Objectives : Spontaneous adverse drug reaction (ADR) reporting by medical institutions is increasingly promoted for collection of drug safety information. Encouraging hospital pharmacists to collect and report ADRs to the regulatory authorities and pharmaceutical companies through the Risk Management Plan (RMP) -assisted hospital pharmacy work would lead to the provision of new information to ensure appropriate use and contribute to new proposals for safety measures. Adjusting RMPs, as a repository of drug-associated risks, to use in the clinical settings would allow their efficient use in adverse drug reaction monitoring. The aim of the study was to build an RMP-based ADR monitoring system and implement this system in electronic medical record (EMR) system to bring about the efficient collection of drug safety information and contribute to pharmacovigilance activities. **Methods:** An RMP database was built and contains 429 risks of 35 drug products. RMP templates prepared for all drugs with an RMP were implemented in EMR system. **Results:** RMP templates were used on 5 drug products in 123 patients from January 2016 to October 2017. The patients with a suspected ADR had 194 events of any Common Terminology Criteria for Adverse Events (CTCAE) grade and 7 events of CTCAE grade 3 or higher. Five ADR reports were submitted to the regulatory authority for the patients with a suspected serious ADR. **Conclusion:** We successfully built an RMP-based ADR monitoring system and implemented it in EMR system to bring about the efficient collection of drug safety information and contribute to pharmacovigilance activities.

Keywords : Risk management plan, adverse drug reaction

INTRODUCTION

Since 2013, pharmaceutical companies in Japan have been required to formulate risk management plans (RMPs) as a component of their drug safety activities. In a Japanese context, an RMP is a document of summary, for an individual drug; (1) important adverse drug reactions and missing information with a clear or suspected relationship to the drug (safety specification), (2) information-collection activities conducted following marketing (pharmacovigilance activities), and (3) efforts to reduce the risks associated with the drug, such as providing information to healthcare professionals and establishing conditions for use (risk minimization activities). The risks listed in the safety specification in item 1 are classified into the three categories of "important identified risks", "important potential risks", and "important missing information" per the International Conference

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on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use（ICH）E2E guideline [1]. The purpose of an RMP is to enhance pharmacovigilance activities through the broad sharing of drug risk management activities by the pharmaceutical company and healthcare professionals. The Ministry of Health, Labour, and Welfare requires that healthcare professionals are made aware of the information in RMPs to allow them to understand the risks associated with the drug and the status of safety measures for those risks for utilization in the appropriate use of the drug [2]. To facilitate pharmacovigilance measures, medical institutions, the pharmaceutical company, and the regulatory authorities must engage together in RMP-based activities.

The Ministry of Health, Labour, and Welfare, Japan, issues notifications to facilitate the use of RMPs at medical institutions [3]. Under these notifications, healthcare professionals are required to contribute to pharmacovigilance activities. The Japanese Society of Hospital Pharmacists issued "On the Use of Drug Risk Management Plans in the Work of Hospital Pharmacists" [4]. This document urges hospital pharmacists to understand RMPs, which detail drug-associated risks and the status of safety measures implemented for those risks, and create systems to utilize this information in their medical institution so as to facilitate the proper use of drugs and contribute to ensuring safety [5]. Spontaneous adverse drug reaction reporting by medical institutions is increasingly promoted under the pharmaceuticals and medical devices safety information reporting system established in Article 68 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. Encouraging hospital pharmacists to collect drug safety information and report this information to the regulatory authorities and pharmaceutical companies through their RMP-assisted hospital pharmacy work would lead to the provision of new information to ensure appropriate use and contribute to new proposals for safety measures. Adjusting RMPs, as a repository of drug-associated risks, to use in the clinical settings would allow their efficient use in adverse drug reaction monitoring. The literature, however, contains no mention of efforts to use RMPs at medical institutions as proposed above.

The objective of the study was to build an RMP-based adverse drug reaction monitoring system and implement this system in electronic medical record system to bring about the efficient collection of drug safety information and contribute to pharmacovigilance activities.

METHODS

(1) Construction of RMP Database

An RMP database was built using Microsoft Access® 2013. A total of 429 risks were extracted from the important identified risks, important potential risks, and important missing information in the safety specifications (risk names) of 35 drug products with an implemented RMP as of January 2016. Then, the followings were created: (1) table of risk names (risk table), (2) table linking adverse events corresponding to risk names to terms in Common Terminology Criteria for Adverse Events (CTCAE) Japan Clinical Oncology Group Japanese version 4.0 (risk-CTCAE/symptom table), (3) table linking drug names to the risk names for the respective drugs (drug-risk table), and (4) table linking CTCAE terms to grades (CTCAE table). When there was no corresponding CTCAE term for a risk name, a symptom related to the risk name was established based on patient-targeted pharmaceutical guides prepared by the pharmaceutical company [6]. Then, the followings were created: table linking risk names to symptoms (merged as risk-CTCAE/ symptom table) and (5) list of all symptoms in the patient-targeted pharmaceutical guide for 35 drugs (symptom table).

(2) Creation of RMP Templates

A tool for creating RMP templates based on the RMP database was made. Creating RMP templates, a given drug may be selected using the query function of Microsoft Access® 2013 to output a table containing the risk names and corresponding CTCAE terms and grades for that drug (Table 1). These tables, prepared for all drugs with

Table 1. Portion of the RMP template for nivolumab

RMP terms	CTCAE terms/symptoms	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Intestinal Lung Disease	Shortness of breath	No	Yes			
	Dry cough	No	Yes			
	Fever	No	Yes			
Myasthenia gravis	Myalgia	No	Yes			
	Feeling of weakness	No	Yes			
	Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Colitis	Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline;	Life-threatening consequences; urgent intervention indicated	Death

an RMP, were implemented as RMP templates in electronic medical record system. It allows healthcare professionals in the hospital to conduct adverse drug reaction monitoring based on RMP. The system was configured so that the results of adverse drug reaction monitoring could be recorded in electronic medical records in tabular format.

(3) Use of the RMP Templates

Pharmacists employed by Miyagi Cancer Center began using the RMP templates in January 2016 to evaluate the adverse drug reactions reported during patient encounters. The adverse drug reaction cases were collected from January 2016 to October 2017. Adverse drug reactions judged to be serious were reported to the regulatory authority as required under the pharmaceuticals and medical devices safety information reporting system.

(4) Ethics approval

This study was approved by the ethics committee of Miyagi Cancer Center（2018-061）, and the requirement to obtain informed consent was waived.

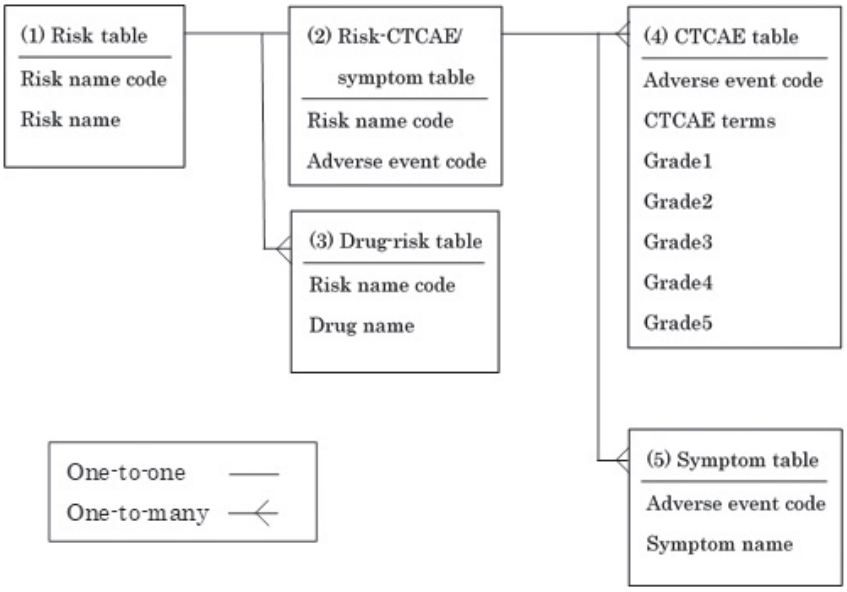

Figure 1. Entity-relationship diagram of the RMP database

RESULTS

(1) Construction of RMP Database

An entity-relationship diagram of the RMP database is shown in Figure 1. The information contained in the tables that make up the RMP database is updated whenever an RMP is created for a new drug or an existing RMP is updated.

(2) Creation of RMP Templates

A portion of the RMP template of nivolumab implemented in electronic medical records is shown in Figure 2. Radio buttons and other controls allow operators of all occupations and levels of clinical experience to conveniently assess grades according to set criteria.

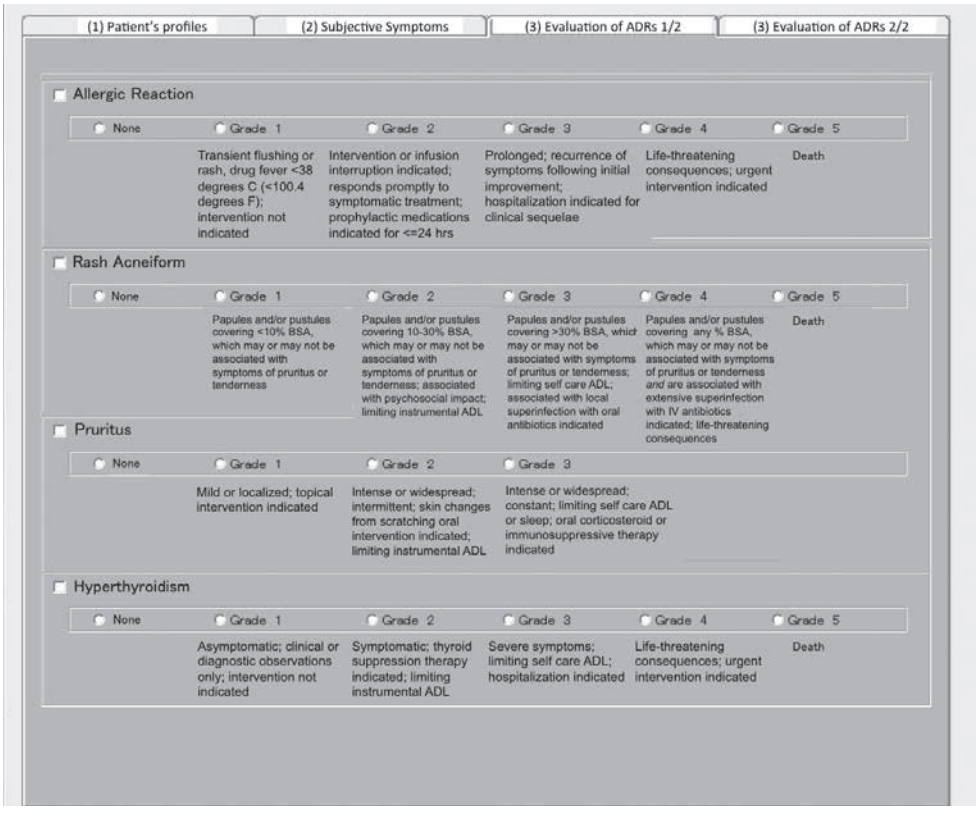

Figure 2. Portion of the RMP template for nivolumab implemented in electronic medical record system

(3) Use of RMP Templates

The adverse drug reaction monitoring system created in 1 and 2 above was used on 5 drug products in 123 patients（10 patients using a fluoropyrimidine drugs, 73 patients using nivolumab, 34 patients using pembrolizumab, 4 patients using ramucirumab, and 2 patients using lenvatinib）from January 2016 to October 2017. The patients with a suspected adverse drug reaction had 194 events of any CTCAE grade（23 for a fluoropyrimidine drugs, 106 for nivolumab, 47 for pembrolizumab, 12 for ramucirumab, and 6 for lenvatinib）and 7 events of CTCAE grade 3 or higher（2 for a fluoropyrimidine drugs, 1 for nivolumab, 2 for pembrolizumab, and 2 for lenvatinib）（Table 2）. Five adverse drug

Table 2. Patients with suspected adverse drug reactions extracted with the RMP templates（n=123）

Drug name	Adverse drug reaction（suspected）	All grades（patients）	Grade 3 or higher（patients）
Fluoropyrimidine drugs	Palmar-plantar erythrodysesthesia syndrome	4	1
	Paronychia	2	1
	Lacrimation	3	0
	Dry skin	6	0
	Oral mucositis	2	0
	Diarrhea	4	0
	Nausea	2	0
Nivolumab	Allergic reactions	6	0
	Acne-like rash	30	0
	Pruritus	29	1
	Hyperthyroidism	8	0
	Hypothyroidism	11	0
	Increased ALT	10	0
	Increased AST	9	0
	Colitis	3	0
Pembrolizumab	Renal impairment	4	0
	Acne-like rash	11	1
	Pruritus	12	1
	Hyperthyroidism	5	0
	Hypothyroidism	3	0
	Increased ALT	5	0
	Increased AST	6	0
	Colitis	1	0
Ramucirumab	Hypertension	4	0
	Diarrhea	1	0
	Proteinuria	2	0
	Epistaxis	1	0
	Alopecia	3	0
	Nausea	1	0
Lenvatinib	Palmar-plantar erythrodysesthesia syndrome	1	0
	Hypertension	2	2
	Diarrhea	1	0
	Proteinuria	1	0
	Epistaxis	1	0

reaction reports were submitted to the regulatory authority for the patients with a suspected serious adverse drug reaction（4 for nivolumab and 1 for pembrolizumab）（Table 3）. Since approximately 60% of the patients surveyed in the present study were using nivolumab, an immune checkpoint inhibitor, we focused on hypothyroidism, which occurs relatively frequently as an immune-related adverse event. The time from the start of treatment to the detection of adverse events and the grade of the first incident were studied in 11 patients who developed hypothyroidism. The results showed that the median time to detection of adverse events was 67 days（interquartile range（IQR）: 59.5-75.5 days）, 9 patients（82%）were Grade 1 and 2 patients（18%）were Grade 2, none of which required discontinuation of treatment.

Table 3. Patients with adverse drug reaction reported to the regulatory authority

Drug name	Adverse drug reaction（suspected）
Nivolumab	Hyperthyroidism, hypothyroidism
Nivolumab	Rhabdomyolysis, Stevens-Johnson syndrome
Nivolumab	Hyperthyroidism
Nivolumab	Pancreatitis
Pembrolizumab	Myasthenia gravis, diabetes insipidus

DISCUSSION

In this study, an RMP-based adverse drug reaction monitoring system was built and implemented in electronic medical record system to allow pharmacists to identify adverse drug reactions and submit adverse drug reaction reports to the regulatory authority. By operating in electronic medical record system, this adverse drug reaction monitoring system allows not only the collection of adverse drug reaction and other safety information associated with patient information, but also adverse drug reactions to be followed over time and accumulated data to be output and modified. Adverse drug reaction data collected over time helps the preparation of adverse drug reaction reports to be submitted to the regulatory authority and should also prove useful to collect data in observational studies and clinical trials. RMP templates are the central actor in the adverse drug reaction monitoring system built in this study. A previous investigation found that introducing templates for electronic medical records enables precise, clear, and fast entries [7]. Since the use of an adverse drug reaction monitoring system at medical institutions allows healthcare professionals with any level of clinical experience to efficiently extract adverse drug reaction information and immediately make corresponding entries in medical records, monitoring systems should be even more useful for outpatient care, which demands rapid assessments of adverse drug reactions and the sharing of information across disciplines. The system enables adverse drug reactions to be assessed across different medical institutions and regulatory authorities because it uses existing assessment criteria for adverse drug reactions.

Developed using Microsoft Access® 2013

（Microsoft Corp., Redmond, WA, USA）, this system could be relatively inexpensively introduced even at medical institutions with minimal information technology infrastructure. Tables that link drugs, RMP risks, adverse events, and symptoms must be prepared to allow the adverse drug reaction monitoring system to operate. The RMPs now available for 324 drugs are published only in PDF format, which does not allow the information to be extracted as plain text. This poses a large hurdle for initial database construction. The risk names they contain, moreover, are not uniformly Medical Dictionary for Regulatory Activities/ Japanese version（MedDRA/J）terms: terminology varies among RMPs. The tasks of addressing the discrepancies among these risk names and then matching them to corresponding CTCAE terms and symptoms would be time consuming and could be affected by operator subjectivity. These issues would be solved if the regulatory authorities standardized RMP entries and made the data they contain easily extractable by secondary users.

We established this system to monitor adverse drug reactions to anticancer drugs. The system allowed us to identify and report five serious immune-related adverse events specific to the immune checkpoint inhibitor nivolumab, which was developed and first approved in Japan under the pharmaceuticals and medical devices safety information reporting system. In addition, we surveyed the time from the start of treatment to the detection of nivolumab-induced hypothyroidism and the grade of the first incident. Using the Japanese Adverse Drug Events Reporting database, which includes a large number of serious adverse drug reactions, the median duration of nivolumab-induced hypothyroidism was 80.5 days（IQR: 44.8-133.3 days）[8]. Although this study was conducted in a small number of cases, it was suggested that the use of our template may allow for the detection of non-serious side effects at a relatively early phase, and may contribute to the prevention of serious adverse reactions and continuation of treatment.

Since Japan has overcome its drug-lag problem and drugs are now developed and approved in the country at the same pace as elsewhere, tools developed from the information integrated into RMPs are needed to help pharmacists in Japan closely monitor adverse drug reactions and create drug safety information. Pharmacovigilance, which involves the monitoring of safety from drug development through the postmarketing phase to ensure drug safety, is defined by the World Health Organization（WHO）as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”[9]. Proper pharmacovigilance requires a safety specification to be prepared and a pharmacovigilance plan and risk minimization measures to be developed while clinical trials are underway. Under the pharmacovigilance plan, drug safety information is collected and the causal relationship of adverse events to the drug in question is evaluated along with severity to monitor for new risks arising after marketing. Appropriate risk minimization measures must be considered for any new potential risks detected. Our adverse drug reaction monitoring system would be well-suited to the collection of postmarketing drug safety information as well as risk monitoring activities in pharmacovigilance programs.

CONCLUSION

We successfully built an RMP-based adverse drug reaction monitoring system and implemented it in electronic medical record system to bring about the efficient collection of drug safety information and contribute to pharmacovigilance activities.

Declarations

Funding

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Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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