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Research Paper

Platinum Agent-Induced Hypersensitivity Reactions: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS

Toshiyuki Sakaeda [1]✉, Kaori Kadoyama [1], Hiroaki Yabuuchi [2,3], Satoshi Niijima [2], Kyoko Seki [4], Yukinari Shiraishi [4] and Yasushi Okuno [2, 3]✉

1. Center for Development of Integrative Education in Pharmacy and Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan
2. Department of Systems Biosciences for Drug Discovery, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan
3. Kyoto Constella Technologies Co., Ltd., Kyoto 604-8156, Japan
4. Department of Pharmacy, Japan Labour Health and Welfare Organization, Kobe Rosai Hospital, Kobe 651-0053, Japan

✉ Corresponding author: Toshiyuki Sakaeda, Ph.D., Center for Development of Integrative Education in Pharmacy and Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan, Tel: +81-75-753-9560, Fax: +81-75-753-4502, e-mail: sakaedat@pharm.kyoto-u.ac.jp; Yasushi Okuno, Ph.D., Department of Systems Biosciences for Drug Discovery, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan, Tel&Fax: +81-75-753-4559, e-mail: okuno@pharm.kyoto-u.ac.jp

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Abstract

Objective: Adverse event reports (AERs) submitted to the US Food and Drug Administration (FDA) were reviewed to confirm the platinum agent-associated mild, severe, and lethal hypersensitivity reactions.

Methods: Authorized pharmacovigilance tools were used for quantitative signal detection, including the proportional reporting ratio, the reporting odds ratio, the information component given by a Bayesian confidence propagation neural network, and the empirical Bayes geometric mean. Excess2, given by the multi-item gamma Poisson Shrinker algorithm, was used to evaluate the effects of dexamethasone and diphenhydramine on oxaliplatin-induced hypersensitivity reactions.

Results: Based on 1,644,220 AERs from 2004 to 2009, carboplatin and oxaliplatin proved to cause mild, severe, and lethal hypersensitivity reactions, whereas cisplatin did not. Dexamethasone affected oxaliplatin-induced mild hypersensitivity reactions, but had lesser effects on severe and lethal reactions. The effects of diphenhydramine were not confirmed.

Conclusion: The FDA's adverse event reporting system, AERS, with optimized data mining tools is useful to authorize potential associations between platinum agents and hypersensitivity reactions.

Key words: adverse event, AERS, platinum agent, hypersensitivity

Introduction

The treatment of metastatic colorectal cancer has progressed significantly over the past 20 years, and currently the FOLFIRI or FOLFOX regimen [1-4], with or without a targeted monoclonal antibody, is the standard treatment [5-8], consisting of the injection of a bolus of 5-fluorouracil (5-FU), irinotecan or oxali-

platin (L-OHP), and the infusion of 5-FU/leucovorin, respectively. Future improvements will likely require the incorporation of or substitution with a novel anticancer drug, personalization based on genetic profiling, or pharmacokinetically-guided administration.

Hypersensitivity reactions are a well-known complication of the use of the platinum agents, cisplatin (CDDP) and carboplatin (CBDCA) [9-12]. L-OHP, a third-generation platinum agent, has also been increasingly recognized to cause hypersensitivity reactions [13-16], but the incidence still varies in reports [17-25]. It is difficult to evaluate the exact prevalence of these reactions, presumably because their definition is vast and pathogenic mechanisms are still vague, but L-OHP-induced hypersensitivity can be classified into relatively acute severe anaphylaxes and delayed mild allergic reactions [13-16]. A reduction of the infusion rate and the administration of steroids and/or antihistamines are used to treat both for acute and delayed hypersensitivity reactions, and discontinuation is strongly suggested immediately upon the development of acute reactions [13-16]. However, large-scale validation is still awaited.

In this study, adverse event reports (AERs) submitted to the US Food and Drug Administration (FDA) were reviewed to confirm the platinum agent-associated mild, severe, and lethal hypersensitivity reactions. This data base relies on spontaneous reports to the FDA generated by health professionals, consumers, and manufacturers, and the system is referred to as the Adverse Event Reporting System (AERS). The structure of AERS is in compliance with international safety reporting guidance, ICH E2B. Recently, the AERS database has been used for evaluation of safety profiles of statins [26-29], rofecoxib [30], topical bovine thrombin [31] and infliximab [32]. Here, the effects of dexamethasone and diphenhydramine on L-OHP-induced reactions were also evaluated to suggest a management strategy for patients with hypersensitivity reactions. The effects of bevacizumab, often used with L-OHP, were also evaluated.

Methods

The AERS database covers several million case reports on adverse events. Pharmacovigilance analysis aims to search for previously unknown patterns and automatically detect important signals, i.e., drug-associated adverse events, from such a large database. Recently developed data mining tools for pharmacovigilance have been successful at detecting signals that could not be found by individual case reviews and that warrant further investigation together with continuous surveillance. For this reason, data mining tools are being routinely used for pharmacovigilance, supporting signal detection and decision-making at companies, regulatory agencies, and pharmacovigilance centers [33-39]. Despite some limitations inherent to spontaneous reporting, the AERS database is a rich resource and the data mining tools described below provide a powerful means of identifying potential associations between drugs and adverse events.

Data sources

Input data for this study were taken from the public release of the FDA's AERS database, which covers the period from the first quarter of 2004 through the end of 2009. The database consists of 7 data sets; patient demographic and administrative information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). The adverse events in REAC are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Prior to analysis, all drug names were unified into generic names by a text-mining approach, because AERS permits the registering of arbitrary drug names, including trade names and abbreviations. For the batch conversion of drug names, reliable drug databases, e.g., FDA Orange Book, were utilized as a dictionary. Spelling errors were detected by GNU Aspell and carefully confirmed by working pharmacists. Furthermore, drug names which failed to receive generic names were manually converted to proper names. Foods, beverages, treatments (e.g. X-ray radiation), and unspecified names (e.g., beta-blockers) were omitted for this study. Duplicated reports were deleted according to FDA's recommendation of adopting the most recent CASE number (as described in one of the downloaded files, 'Asc_nts.doc' from the web-site of the FDA AERS database), resulting in the reduction of the number of AERs from 2,231,029 to 1,644,220.

Definition of adverse events

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0, AERs with PT10020751/ hypersensitivity in REAC were adopted as the reports on mild hypersensitivity reactions, in which 19 lower level terms (LLTs) were assigned in MedDRA v13.0, including LLT10000656/acute allergic reaction, LLT10001718/allergic reaction, LLT10020756/ hypersensitivity reaction, LLT10020759/

hypersensitivity symptom, LLT10038195/red neck syndrome, and LLT10046305/upper respiratory tract hypersensitivity reaction (site unspecified). AERs with PT10011906/death (with 13 LLT) or death terms in OUTC were excluded for mild hypersensitivity reactions. AERs with PT10002198/anaphylactic reaction were adopted as the reports on severe hypersensitivity reactions, in which 13 LLTs were assigned, including LLT10000663/acute anaphylactic reaction and LLT10002218/anaphylaxis. AERs both with PT10020751, and PT10011906 or death terms in OUTC were adopted as the reports on lethal hypersensitivity reactions. Of note, LLT10001718/allergic reaction and LLT10002218/anaphylaxis are assigned as allergic reactions and anaphylaxis in the NCI-CTCAE v4.0, respectively, and PTs in their higher levels were used in this study.

Data mining

In pharmacovigilance analysis, data mining algorithms have been developed to identify drug-associated adverse events as signals that are reported more frequently than expected by estimating expected reporting frequencies on the basis of information on all drugs and all events in the database [37-39]. For example, the proportional reporting ratio (PRR) [33], the reporting odds ratio (ROR) [34], the information component (IC) [35], and the empirical Bayes geometric mean (EBGM) [36] are widely used, and indeed, the PRR is currently used by the Medicines and Healthcare products Regulatory Agency (MHRA), UK, the ROR by the Netherlands Pharmacovigilance Centre, the IC by the World Health Organization (WHO), and the EBGM by the FDA.

All of these algorithms extract decision rules for signal detection and/or calculate scores to measure the associations between drugs and adverse events from a two-by-two frequency table of counts that involve the presence or absence of a particular drug and a particular event occurring in case reports. These algorithms, however, differ from one another in that the PRR and ROR are frequentist (non-Bayesian), whereas the IC and EBGM are Bayesian. In this section, only the scoring thresholds used in the present study are given, and the reader is referred to review articles for details [37-39].

For the PRR, a given drug-adverse event pair was defined as a signal, if the event count ≥ 3, and the PRR ≥ 2.0 with an associated chi-square value ≥ 4.0 [33], and for the ROR, if the lower bound of the 95% two-sided confidence interval (CI) of ROR exceeded 1 [34]. For the IC, IC025, a criterion indicating the lower bound of the 95% two-sided CI of the IC, was adopted, and a IC025 value exceeding 0 was defined as a signal [35]. Lastly, for the EBGM, EB05 ≥ 2.0 was set as a threshold for signal detection, where EB05 is interpreted as a lower one-sided 95% confidence limit of EBGM [36].

The AERS database is also a valuable resource for exploring drug-drug interactions. Here, we are interested in how the co-administration of dexamethasone, diphenhydramine, and bevacizumab would affect L-OHP-induced mild, severe, and lethal hypersensitivity reactions, although the database does not provide the information on the timing of co-administration. To analyze such interactions, case reports on L-OHP were classified according to whether they also involved one of the three drugs. Any association among the interactions was then assessed using Excess2, a statistical index of the multi-item gamma Poisson shrinker (MGPS) algorithm [36].

Results

AERs in which CDDP, CBDCA, or L-OHP was the principal offending agent are summarized in Tables 1-3, and numbered 44,321, 39,653, and 33,194 of 1,644,220, respectively. Reports of mild, severe, and lethal hypersensitivity reactions numbered 43,288, 18,225, and 2,397, respectively.

CBDCA was administered in 229 of 43,288 AERs of mild, 72 of 18,225 AERs of severe, and 12 of 2,397 AERs of lethal hypersensitivity reactions (Table 2). L-OHP was administered in 126, 60 and 10, respectively (Table 3). The signals were detected for CBDCA and L-OHP by either the PRR, ROR, IC or EBGM, but no signal was suggested for CDDP (Table 1). The sensitivity was higher for ROR or IC, whereas lower for EBGM.

The effects of the co-administration of dexamethasone on L-OHP-induced hypersensitivity reactions are summarized in Table 4. The values obtained with Excess2 were 18.66, 1.19 and -0.44, respectively, indicating that dexamethasone was more effective against mild than severe or lethal reactions. The effects of diphenhydramine were also examined, but no signal was detected (data not shown). The data on the co-administration of bevacizumab is listed in Table 5. Values of Excess2 were 0.28, 5.38 and -5.65, respectively, and suggesting an effect of bevacizumab on severe L-OHP-induced reactions.

Table 1. Signal detection for CDDP-associated mild, severe and lethal hypersensitivity reactions

	Mild 43,288	Severe 18,225	Lethal 2,397
No.of AERs	38	29	5
PRR (kai2)	0.436 (27.256)	0.790 (1.412)	1.036 (0.022)
ROR (95% two-sided CI)	0.435 (0.317, 0.553)	0.790 (0.549, 1.031)	1.036 (0.431, 1.641)
IC (95% two-sided CI)	-1.195 (-1.651, -0.739)	-0.353 (-0.875, 0.169)	-0.081 (-1.287, 1.125)
EBGM (95% one-sided CI)	0.441 (0.337)	0.781 (0.574)	0.907 (0.455)

Total number of adverse event reports (AERs) accompanied with CDDP administration was 44,321. Reports of mild, severe and lethal hypersensitivity reactions numbered 43,288, 18,225 and 2,397, respectively. PRR: the proportional reporting ratio [33], ROR: the reporting odds ratio [34], IC: the information component [35], EBGM: the empirical Bayes geometric mean [36]. There was no signal for CDDP-associated mild, severe and lethal hypersensitivity reactions (see "Methods" for the criteria of detection).

Table 2. Signal detection for CBDCA-associated mild, severe and lethal hypersensitivity reactions

	Mild 43,288	Severe 18,225	Lethal 2,397
No.of AERs	229	72	12
PRR (kai2)	2.949 * (291.792)	2.196 * (45.698)	2.780 * (11.975)
ROR (95% two-sided CI)	2.959 * (2.598, 3.320)	2.201 * (1.746, 2.656)	2.789 * (1.582, 3.996)
IC (95% two-sided CI)	1.539 * (1.352, 1.726)	1.100 * (0.767, 1.433)	1.233 * (0.432, 2.034)
EBGM (95% one-sided CI)	2.880 * (2.580)	2.097 (1.723)	2.079 (1.288)

Total number of adverse event reports (AERs) accompanied with CBDCA administrations was 39,653. Reports of mild, severe and lethal hypersensitivity reactions numbered 43,288, 18,225 and 2,397, respectively. PRR: the proportional reporting ratio [33], ROR: the reporting odds ratio [34], IC: the information component [35], EBGM: the empirical Bayes geometric mean [36]. *: signal detected, see "Methods" for the criteria of detection.

Table 3. Signal detection for L-OHP-associated mild, severe and lethal hypersensitivity reactions

	Mild 43,288	Severe 18,225	Lethal 2,397
No.of AERs	126	60	10
PRR (kai2)	1.934 (55.797)	2.186 * (37.412)	2.768 * (9.604)
ROR (95% two-sided CI)	1.937 * (1.626, 2.248)	2.190 * (1.699, 2.681)	2.775 * (1.491, 4.059)
IC (95% two-sided CI)	0.933 * (0.681, 1.185)	1.087 * (0.723, 1.451)	1.187 * (0.312, 2.062)
EBGM (95% one-sided CI)	1.888 (1.628)	2.070 (1.669)	1.983 (1.178)

Total number of adverse event reports (AERs) accompanied with L-OHP administrations was 33,194. Reports of mild, severe and lethal hypersensitivity reactions numbered 43,288, 18,225 and 2,397, respectively. PRR: the proportional reporting ratio [33], ROR: the reporting odds ratio [34], IC: the information component [35], EBGM: the empirical Bayes geometric mean [36]. *: signal detected, see "Methods" for the criteria of detection.

Table 4. Effect of co-administration of dexamethasone on L-OHP-associated hypersensitivity reactions

	L-OHP	dexamethasone	Hypersensitivity		Excess2
			yes	no	
Mild	yes	yes	40	4,774	18.66
	yes	no	469	172,768	
	no	yes	1,884	924,995	
	no	no	132,784	184,631,220	
Severe	yes	yes	13	4,801	1.19
	yes	no	214	173,023	
	no	yes	919	925,960	
	no	no	53,827	184,710,177	
Lethal	yes	yes	6	4,808	-0.44
	yes	no	54	173,183	
	no	yes	393	926,486	
	no	no	13,287	184,750,717	

The numbers of L-OHP-associated hypersensitivity reactions are listed. The interaction was assessed using Excess2, a statistical index of the multi-item gamma Poisson shrinker (MGPS) algorithm [36]. The data suggested that dexamethasone affected mild L-OHP-induced hypersensitivity reactions, but had lesser effects on severe and lethal reactions.

Table 5. Effect of co-administration of bevacizumab on L-OHP-associated hypersensitivity reactions

	L-OHP	bevacizumab	Hypersensitivity		Excess2
			yes	no	
Mild	yes	yes	35	11,943	0.28
	yes	no	286	200,959	
	no	yes	474	165,599	
	no	no	134,382	185,355,256	
Severe	yes	yes	20	11,958	5.38
	yes	no	103	201,142	
	no	yes	207	165,866	
	no	no	54,643	185,434,995	
Lethal	yes	yes	4	11,974	-5.65
	yes	no	45	201,200	
	no	yes	56	166,017	
	no	no	13,635	185,476,003	

The numbers of L-OHP-associated hypersensitivity reactions are listed. The interaction was assessed using Excess2, a statistical index of the multi-item gamma Poisson shrinker (MGPS) algorithm [36]. The data suggested that bevacizumab possibly affected severe L-OHP-induced hypersensitivity reactions.

Discussion

Although the exact mechanism by which platinum agents cause hypersensitivity reactions remains unclear, the agents are thought to induce a type I response mediated by IgE, followed by the release of histamine and cytokines, since reactions usually occur after multiple infusions [13-16]. Recent studies have suggested the involvement of a type IV reaction, i.e., T-cell-mediated production of cytokines, such as tumor necrosis factor-alpha and interleukin-6, especially for CDDP and CBDCA [13-16]. As far as L-OHP is concerned, most reactions are thought to be of type I, but reports of hemolysis and thrombocytopenia suggest a type II reaction, and chronic urticaria, joint pain and proteinuria can be attributed to a type III reaction [13-16]. The incidence of hypersensitivity reactions varies in reports, and this study was conducted to confirm the platinum agent-associated mild, severe, and lethal hypersensitivity reactions. Here, using an extremely large number of AERs submitted to the FDA with authorized data mining tools, CBDCA and

L-OHP proved to cause mild, severe, and lethal hypersensitivity reactions, whereas CDDP did not.

Spontaneous reports of suspected adverse events are a valuable tool. However, this database has its limitations [37]. First, the data occasionally contain misspelling and miswords, although the structure of AERS is in compliance with the international safety reporting guidance. Second, the system was started more than 10 years ago, and reporting patterns have changed over time. Third, the adverse events are coded using hierarchical terms of PTs of MedDRA, and changes in terminology over time also might affect the quality of the database. Last, there are a number of duplicate entries in the database. To overcome problems with data quality, we manually corrected mistakes in the data entities and deleted duplicates according to FDA's recommended method. A long-term discussion on pharmacovigilance strategies with large numbers of spontaneous reports resulted in the quantitative signal detection indices PRR, ROR, IC and EBGM. Comparisons in terms of specificity showed that none of these indices is universally better than the others [34, 37, 38], but EBGM is of lowest sensitivity in this study (Tables 2, 3).

Since 1998, the FDA has been exploring the MGPS program, which evaluates the signals for pairs and higher-order [35]. This program is used to detect possible synergistic interactions between drugs, i.e., drug-drug interaction. With an index of Excess2, the effects of dexamethasone and diphenhydramine on L-OHP-induced hypersensitivity reactions were evaluated to suggest the best patient management strategy. It was suggested that the co-administration of dexamethasone affected mild L-OHP-induced reactions more effectively, than severe or lethal reactions (Table 4). Here, the effects of diphenhydramine were not confirmed, but unexpectedly, it was suggested that bevacizumab affected L-OHP-induced severe reactions. It is noted that the database does not provide the information on the timing of co-administration. Additionally, we do not have the criteria, e.g., threshold value, of Excess2 to detect an unknown drug-drug interaction, and the calibration using many known drug-drug interactions would be necessary.

In conclusion, AERs submitted to the FDA were reviewed to confirm the platinum agent-associated mild, severe, and lethal hypersensitivity reactions. Authorized pharmacovigilance tools were used for quantitative signal detection, and the effects of dexamethasone and diphenhydramine on L-OHP-induced hypersensitivity reactions were also evaluated. Based on 1,644,220 AERs from 2004 to 2009, CBDCA and L-OHP proved to cause mild, severe, and lethal hypersensitivity reactions, whereas CDDP did not. Dexamethasone affected L-OHP-induced mild hypersensitivity reactions, but had lesser effects on severe and lethal reactions.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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