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Research Paper

Adverse Event Profiles of Platinum Agents: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS, and Reproducibility of Clinical Observations

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Abstract

Objective: Adverse event reports (AERs) submitted to the US Food and Drug Administration (FDA) were reviewed to confirm platinum agent-associated adverse events, and to clarify the rank-order of these drugs in terms of susceptibility.

Methods: After a revision of arbitrary drug names and the deletion of duplicated submissions, AERs involving cisplatin (CDDP), carboplatin (CBDCA), or oxaliplatin (L-OHP) were analyzed. Authorized pharmacovigilance tools were used for the quantitative detection of signals, i.e., drug-associated adverse events, 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.

Results: Based on 1,644,220 AERs from 2004 to 2009, CDDP, CBDCA, and L-OHP all proved to cause nausea, vomiting, acute renal failure, neutropenia, thrombocytopenia, and peripheral sensory neuropathy. Higher susceptibility to nausea was found for CDDP than CBDCA and L-OHP. Acute renal failure was also more predominant for CDDP, and CBDCA did not increase the blood level of creatinine. A stronger association with thrombocytopenia was suggested for CBDCA. Susceptibility to peripheral sensory neuropathy was greatest for L-OHP, but less extensive for CDDP and CBDCA.

Conclusion: The results obtained herein were consistent with clinical observations, suggesting the usefulness of the FDA's adverse event reporting system, AERS, and the data mining method used herein.

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

Introduction

The chemotherapeutic treatment of solid tumors has progressed extensively since the development of the first platinum agent, cisplatin (CDDP), in the 1970s [1]. Although the precise mechanisms by which

CDDP exerts its cytotoxic action has not been fully elucidated, its effects on solid tumors have encouraged CDDP-based clinical protocols, and also the development of new platinum agents [1, 2]. Today, the leading agents include CDDP, carboplatin (CBDCA), and oxaliplatin (L-OHP), which share some structural similarities, but differ in therapeutic use and safety profiles.

Besides acute effects such as gastrointestinal toxicity and myelosuppression, CDDP exerts its most toxic effects on organs, such as the nervous system, the organ of Corti, and the kidneys [2, 3]. The dose-limiting toxicity (DLT) is nephrotoxicity, and osmotic diuresis, a prolongation of infusion time, and dose fractionation have been tried [2-4]. For CBDCA, the DLT is myelosuppression, and the organ toxicity is not as problematic, resulting in the replacement of CDDP with CBDCA in CDDP-based protocols [2, 4]. L-OHP is not nephrotoxic like CBDCA, and only moderately emetogenic, but peripheral sensory neuropathy is its most important toxic effect [2, 4-6].

Previously, adverse event reports (AERs) submitted to the US Food and Drug Administration (FDA) were reviewed to confirm an association between platinum agents and hypersensitivity reactions [7]. This database relies on spontaneous reports to the FDA by health professionals, consumers, and manufacturers, and the system is referred to as the Adverse Event Reporting System (AERS). To evaluate the results quantitatively, authorized pharmacovigilance methods were used for signal detection [8-14], where a signal means a drug-associated adverse event. Here, gastrointestinal toxicity (nausea, vomiting), nephrotoxicity (acute renal failure, an increase in blood creatinine level), myelosuppression (neutropenia, thrombocytopenia) and peripheral sensory neuropathy are focused on as adverse events [1-6]. The rank-order of CDDP, CBDCA, and L-OHP was clarified in terms of susceptibility to these adverse events using statistical indices given by authorized pharmacovigilance methods [8-14].

Methods

Data sources

The data for this study were retrieved 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 data structure of AERS is in compliance with international safety reporting guidance, ICH E2B, consisting 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. Here, version 13.0 of MedDRA was used.

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., the 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.

Data mining

In pharmacovigilance analyses, 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 [12-14]. The proportional reporting ratio (PRR) [8], the reporting odds ratio (ROR) [9], the information component (IC) [10], and the empirical Bayes geometric mean (EBGM) [11] are widely used, and indeed, are currently employed by the Medicines and Healthcare products Regulatory Agency (MHRA), UK, the Netherlands Pharmacovigilance Centre, the World Health Organization (WHO), and the FDA, respectively.

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 [12-14].

For the PRR, a given drug-adverse event pair was defined as a signal, if the event count was 3 or more, and the PRR was 2 or more with an associated chi-square value of 4 or more [8], and for the ROR, if the lower limit of the 95% two-sided confidence interval (CI) of ROR exceeded 1 [9]. For the IC, IC025, a criterion indicating the lower limit of the 95% two-sided CI of the IC, was adopted, and an IC025 value exceeding 0 was defined as a signal [10]. Lastly, for the EBGM, an EB05 of 2 or more was set as a threshold for signal detection, where the EB05 is interpreted as the lower one-sided 95% confidence limit of the EBGM [11]. In this study, AERs were extracted for CDDP, CBDCA, and L-OHP, when the signal was detected by either the PRR, ROR, IC or EBGM.

Results

In total, 884 adverse events were detected as signals for CDDP, 810 for CBDCA, and 732 for L-OHP. The total number was 28,382, 24,835, and 21,168, representing 0.13%, 0.11%, and 0.10% of all co-occurrences, respectively.

Nausea/PT10028813, vomiting/PT10047700, acute renal failure/PT10038436, neutropenia/PT10029354, thrombocytopenia/PT10043554, and peripheral sensory neuropathy/PT10034620 were detected for CDDP, CBDCA, and L-OHP. An increase of blood creatinine level/PT10005483 was detected for CDDP and L-OHP. The statistical data are listed in Tables 1-4. Diarrhea/PT10012735, asthenia/PT10003549, dehydration/PT10012174, and pyrexia/PT10037660 were also detected for all 3 platinum agents (data not shown).

Higher susceptibility to nausea was found for CDDP than CBDCA and L-OHP, but L-OHP caused vomiting equally to CDDP (Table 1). Acute renal failure was also more predominant for CDDP, and no CBDCA-associated increase in blood creatinine level was detected (Table 2). The association with neutropenia was weaker for L-OHP than the others, and a stronger association with thrombocytopenia was suggested for CBDCA (Table 3). Susceptibility to peripheral sensory neuropathy was greatest for L-OHP, but less extensive for CDDP and CBDCA (Table 4).

Discussion

The AERS database covers several million case reports on adverse events. Pharmacovigilance 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, i.e., the PRR, ROR, IC, and EBGM, have been successful at detecting signals that could not be found by individual case reviews and that warrant further investigation together with continuous surveillance. These tools are now used routinely for pharmacovigilance, supporting signal detection and decision-making at companies, regulatory agencies, and pharmacovigilance centers [8-14]. Comparisons of specificity have showed that none of these indices is universally better than the others [9, 12, 13], but EBGM has the lowest sensitivity in this study (Tables 1-4).

Table 1. Signal detection for cisplatin-, carboplatin-, and oxaliplatin-associated gastrointestinal toxicity

	N	PRR (kai2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Nausea					
Cisplatin	1083	1.891 (443.773)	1.895 * (1.784, 2.006)	0.901 * (0.814, 0.988)	1.865 (1.773)
Carboplatin	778	1.511 (131.593)	1.513 * (1.409, 1.616)	0.584 * (0.482, 0.687)	1.497 (1.411)
Oxaliplatin	673	1.562 (133.137)	1.564 * (1.449, 1.679)	0.631 * (0.521, 0.741)	1.546 (1.451)
Vomiting					
Cisplatin	1082	2.777 * (1201.214)	2.787 * (2.624, 2.951)	1.448 * (1.361, 1.535)	2.723 * (2.590)
Carboplatin	695	1.980 (330.798)	1.983 * (1.840, 2.127)	0.970 * (0.862, 1.078)	1.955 (1.836)
Oxaliplatin	743	2.541 * (678.261)	2.547 * (2.368, 2.726)	1.322 * (1.217, 1.427)	2.493 * (2.346)

N: the number of co-occurrences.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Nausea and vomiting were coded as PT10028813 and PT10047700, respectively.

Table 2. Signal detection for cisplatin-, carboplatin-, and oxaliplatin-associated nephrotoxicity

	N	PRR (kai2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Acute renal failure					
Cisplatin	388	1.971 (183.494)	1.975 * (1.787, 2.163)	0.968 * (0.823, 1.112)	1.948 (1.791)
Carboplatin	208	1.177 (5.346)	1.178 * (1.027, 1.328)	0.229 * (0.033, 0.426)	1.169 (1.042)
Oxaliplatin	198	1.339 (16.612)	1.340 * (1.165, 1.515)	0.413 * (0.212, 0.615)	1.327 (1.179)
Increase of blood creatinine level					
Cisplatin	251	2.043 * (132.060)	2.047 * (1.808, 2.286)	1.018 * (0.838, 1.197)	2.012 (1.812)
Carboplatin			not detected		
Oxaliplatin	123	1.334 (9.920)	1.335 * (1.118, 1.551)	0.405 * (0.149, 0.660)	1.316 (1.133)

N: the number of co-occurrences.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Acute renal failure and increase of blood creatinine level were coded as PT10038436 (renal failure acute) and PT10005483 (blood creatinine increased), respectively.

Table 3. Signal detection for cisplatin-, carboplatin-, and oxaliplatin-associated myelosuppression

	N	PRR (kai2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Neutropenia					
Cisplatin	708	6.757 * (3418.410)	6.835 * (6.343, 7.328)	2.724 * (2.616, 2.832)	6.659 * (6.257)
Carboplatin	590	6.287 * (2583.368)	6.346 * (5.848, 6.845)	2.620 * (2.502, 2.738)	6.200 * (5.791)
Oxaliplatin	389	4.935 * (1204.217)	4.964 * (4.491, 5.438)	2.273 * (2.129, 2.418)	4.864 * (4.465)
Thrombocytopenia					
Cisplatin	442	3.373 * (729.638)	3.389 * (3.085, 3.693)	1.735 * (1.599, 1.870)	3.314 * (3.061)
Carboplatin	451	3.852 * (940.462)	3.872 * (3.528, 4.216)	1.923 * (1.789, 2.057)	3.783 * (3.496)
Oxaliplatin	302	3.074 * (417.348)	3.084 * (2.753, 3.415)	1.599 * (1.435, 1.763)	3.009 * (2.734)

N: the number of co-occurrences.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Neutropenia and thrombocytopenia were coded as PT10029354 and PT10043554, respectively.

Table 4. Signal detection for cisplatin-, carboplatin-, and oxaliplatin-associated peripheral sensory neuropathy

	N	PRR (kai2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Cisplatin	17	3.449 * (27.214)	3.467 * (2.151, 4.782)	1.561 * (0.883, 2.240)	2.675 (1.754)
Carboplatin	16	3.629 * (27.936)	3.646 * (2.230, 5.062)	1.609 * (0.910, 2.307)	2.760 (1.775)
Oxaliplatin	34	9.217 * (241.016)	9.332 * (6.651, 12.013)	2.878 * (2.393, 3.363)	9.025 * (6.734)

N: the number of co-occurrences.

PRR: the proportional reporting ratio, ROR: the reporting odds ratio, IC: the information component, EBGM: the empirical Bayes geometric mean.

*: signal detected, and a signal means a drug-associated adverse event (see "Methods" for the criteria of detection).

Peripheral sensory neuropathy was coded as PT10034620.

The AERS database is considered a valuable tool; however, some limitations inherent to spontaneous reporting have been pointed out [12]. 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. What's an urgent need is to verify the usefulness of system we developed by comparing the data obtained and clinical observations, and here, the platinum agent-associated adverse events were analyzed.

CBDCA is thought to be only moderately emetogenic like L-OHP, when compared with CDDP [2]. This clinical observation was demonstrated quantitatively herein; a higher susceptibility to nausea was found for CDDP (Table 1). However, it is strange that L-OHP caused vomiting equally to CDDP, and they might differ in the combination of antiemetic drugs. The DLT of CDDP is nephrotoxicity, which is said to be less common or absent in patients receiving CBDCA or L-OHP [2]. This was also proved here (Table 2). The DLT of CBDCA is myelosuppression, and a stronger association with thrombocytopenia was suggested for CBDCA (Table 3). The most important adverse event of L-OHP is peripheral sensory neuropathy [2], and again this was confirmed in the present study (Table 4). Collectively, the quantitative data obtained herein were consistent with clinical observations, suggesting the usefulness of the AERS database and data mining method, although further extensive examinations should be performed.

In conclusion, AERs submitted to the FDA were reviewed to confirm platinum agent-associated adverse events and to clarify rank-order in terms of susceptibility. Based on 1,644,220 AERs from 2004 to 2009, it was confirmed that CDDP, CBDCA and L-OHP proved to cause nausea, vomiting, acute renal failure, neutropenia, thrombocytopenia and peripheral sensory neuropathy. The rank-order was consistent with clinical observations, suggesting the usefulness of the AERS database and the data mining method used herein.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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