ADVERSE DRUG REACTIONS OF PLATINUM ANALOGS: A REVIEW

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ABSTRACT: *The objective of this study was to summarize recent evidence obtained from Adverse Drug Reactions (ADRs) of platinum analogs and to know what are exactly the most common ADRs in platinum, their frequency, causality, severity, and preventability. A bibliographic search was performed in the following databases: PubMed, ScienceDirect, and Google Scholar, search covering the period 2010 to 2020. The inclusion criteria were as follow original articles that reported platinum effects in humans, articles that discuss the effects of platinum, articles that assessed causality or severity or preventability of platinum agents, and articles published in the last ten years. Animal studies and case reports were excluded. Hence, a systematic review was discussed by identified and analyzed 3 relevant studies. The major adverse drug reactions included vomiting (35.49%) followed by alopecia (22.95 %), nausea (19.4%), anorexia, diarrhea, taste alteration, constipation, tinnitus, abnormal renal, and dizziness. Assessment with Naranjo's Algorithm and WHO assessment scale indicated most ADRs are "possible" than "probable". The result of Hartwig and Siegel scale, most ADRs of platinum analogs showed "moderate" followed by "mild" and "severe". The preventability assessment with modified Schumock and Thornton scale of platinum analogs, most of all showed "definitely preventable" followed by "not preventable" and "probably preventable". Almost all ADRs of platinum are predictable. Platinum analog is not entirely risk-free, as it has several kinds of potential ADRs such as vomiting, alopecia, nausea. Currently, there is a lack of information on platinum ADRs. In the interest of patient safety, sufficiently large prospective studies should be considered to clarify this issue.*

Keywords: Platinum analogs, Adverse drug reactions, Naranjo's Algorithm, WHO assessment scale, Hartwig and Siegel scale, Modified Schumock and Thornton scale

INTRODUCTION

Adverse drug reactions (ADRs) represent an important public health problem(1). The World Health Organization (WHO) defines an ADRs is a drug-related event that is noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function (2). ADRs are believed to be the fourth to the sixth leading cause of death among hospitalized patients (1). Adverse drug reactions are responsible for a number of hospital admissions, increase morbidity, and mortality, and have a significant impact on healthcare costs (3).

Anticancer has a narrow therapeutic index. Inappropriate use will increase suffering, fatal condition, and cause waste of cost (4). Anticancer drugs are among the class of drugs most commonly associated with adverse drug reaction (1). Platinum is one of the drugs used in cancer chemotherapy (4). Cisplatin, carboplatin and oxaliplatin are major contributors to systemic therapy, for a very broad range of malignancies (5). Some researches claim that platinum compounds have a large tendency to cause ADRs (6). Postmarketing surveillance of medicines is essential to detect previously unrecognized adverse effects (7). Most ADRs not reported and lead delays in identifying important reactions of the drug (8). There is a lack of information on the platinum ADRs. Hence, a systematic review needed to know what are exactly the most common ADRs in platinum, their frequency, causality, severity, preventability, and predictability.

METHODS

This study did a systematic review of the published medical literature using the computerized bibliographic databases. A bibliographic search was performed in the following databases: PubMed, ScienceDirect, and Google Scholar, mainly published from the year 2010 to 2020. The search terms were "adverse drug reaction" OR "adverse effects" OR "adverse reaction reporting system" AND "chemotherapy" OR "platinum" OR "cisplatin". No restriction by language or by type of publication.

The inclusion criteria were as follow original articles that reported platinum effects in humans, articles that discuss the effects of platinum, articles that assessed causality or severity or preventability of platinum agents, and articles published in the last ten years. Animal studies and case reports were excluded.

This article evaluated the adverse drug reaction of the platinum agents, data collected on the number of patients, sex, age, indication for use, severity assessment, causality assessment, and preventability assessment. In this review, we used the terminology for adverse drug reactions and adverse effects. Adverse drug reaction was used for adverse effects specific to a drug. The adverse effect is used for an adverse event for which the causal relationship between the intervention and the event is at least a reasonable possibility.

RESULT

The initial search yielded 474 publications (Fig. 1). After excluding the studies and screening abstracts, 460 articles do not meet the inclusion criteria. There were 14 articles possibly relevant articles on platinum adverse drug reaction. After studying full-text articles, there were 11 articles not included in the criteria, consist of 1 article was case report and in vivo in vitro study, 6 articles discussed ADRs from chemotherapy agent, 4 articles did not assess the severity of preventability or causality. Finally, 3 articles on platinum adverse drug reactions were included (6,9,10).

Three articles were analyzed. All of these articles were prospective studies. Three articles discussed platinum adverse drug reactions profile (6,9,10). Out of these 3 articles, the occurrence of platinum adverse drug reactions was reported in 209 patients (Table. 2). 128 of these patients (61.24 %) were women and 81 men (38.75 %). The most common age group that developed the maximum number of ADRs is 41-60 years (56.9%) followed by age

group 21-40 (29.09%) (6,9). One article did not show the age group (10).

Therapeutic indications

Therapeutic indications included malignancies of the lung (9,10), head and neck cancer (9), carcinoma cervix (9,10), oral cavity (10), carcinoma ovary (9,10), carcinoma colon, carcinoma stomach, carcinoma esophagus and osteosarcoma (9). One article did not explain the therapeutic indications (6). Among these therapeutic indications, no articles have shown a specific number of diseases.

Adverse drug reactions

The adverse drug reaction of the whole articles mainly included nausea, anorexia (6,10), vomiting, alopecia, diarrhea, constipation (6,9,10), taste alteration, (9,10). hypocalcemia, salivation (10), tinnitus, headache, dizziness (6,10), myelosuppression, abnormal renal function tests, thrombocytopenia (9). anemia (6,9). Prevalence for chest pain, dry mouth, febrile neutropenia, flatulence, increased SGPT, insomnia, numbness, rashes, itching, joint pain, lethargy is the same. Other ADRs were pigmentation of nail, fever, limb pain and body pain were, nervousness, and mucositis (6). The platinum adverse drug reactions can be consulted in Table 1.

Platinum compound

two of the three articles reviewed have studied cisplatin, carboplatin, and oxaliplatin (6,9). One article studied cisplatin-based chemotherapy (10). Two articles reported the used of single and combined platinum

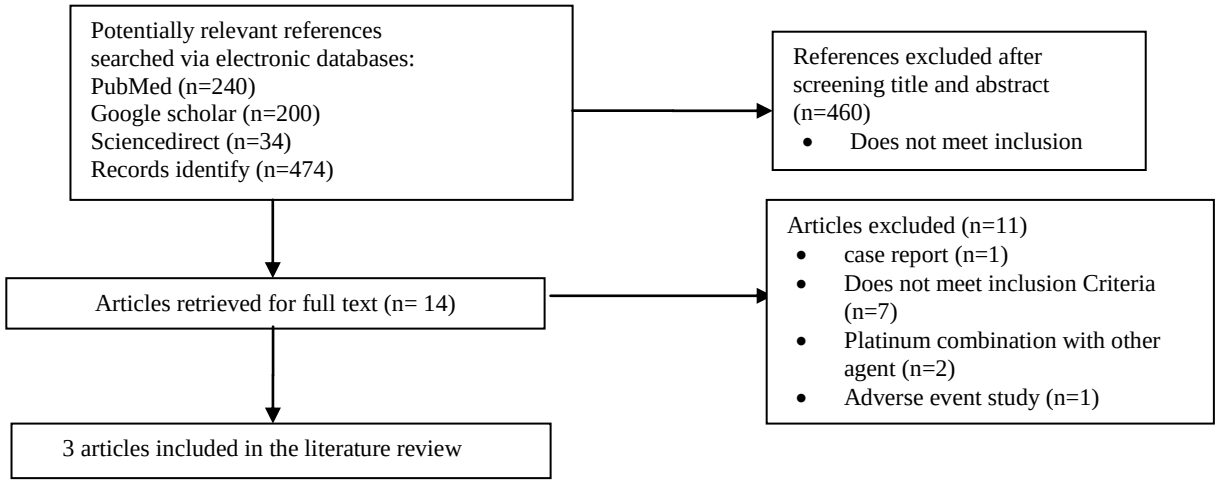

Fig. 1 Flowchart showing article identification and selection. Although 474 studies found, only 15 studies reported assessment (or assessed) adverse drug reaction from the platinum compound. Furthermore, only 3 studies included with our criteria

Causality assessment

Causality assessment (Table. 1) assessed with Naranjo's Algorithm and world health organization (WHO) causality assessment scale (9,10). The result in all patients was stratified by causality assessment. Assessment with WHO causality assessment scale, a total of 48 cases, 69% reactions were possible and 31% were probable (10), not much different, one study showed that 64.6% reaction was probable and 35.4% were possible (9). Another study reported 74.29% ADRs were possible and 25.7% were probable (6). As per Naranjo's algorithm 62% of the reactions were categorized probable (10), and on the other study reported 59.4% ADRs were probable (35.4%). For the possible category, one study showed 38% ADRs were possible(catur) and another study reported 40.6% (9). One study did not use Naranjo's algorithm (6).

Severity assessment

All studies in these articles review used Hartwig and Siegel scale to assess the severity (Table. 1). The treatment used cisplatin-based chemotherapy on 48 cases, the severity from this study got most of the reactions were of less severity categorized mild level 1 severity, but vomiting diarrhea and hypocalcemia were categorized as moderate level 3 severity (10). One study reported the severity of this study was mild-moderate and severe (9), but another article did not get severe (6).

Preventability assessment

Nausea and vomiting belonged to the category of definitely preventable and most of the ADRs category were not preventable in cisplatin-based chemotherapy treatment (10). The treatment with 3 major platinum compounds, it got 47.9% ADRs were definitely preventable, 15.6% were probably preventable and 35.6% ADRs were not preventable (9). Two studies conducted an assessment with a modified Schumock and Thornton scale (9,10) and the other study was not do the preventability assessment (6) (Table 1).

Table 1. Design, treatment, and assessment of the studies

Reference(s)	Design of study, number of ADRs cases	Treatment	Causality assessment, method	Severity assessment, method	Preventability assessment or predictability assessment, method	Most common ADRs (%)
(10)	Prospective (48)	Cisplatin-based chemotherapy	• 69% reaction was possible, 31% were probable, and there was no certain (WHO assessment scale). • 62% of the ADRs were probable, 38% of the ADRs were possible (Naranjo's algorithm).	• Most of the reactions were of less severity categorized mild level 1 severity, vomiting diarrhea, and hypocalcemia were categorized as moderate level 3 severity (Hartwig and Siegel scale).	• Most of the ADRs category were not preventable, nausea and vomiting belonged to the category of definitely preventable (modified Schumock and Thornton scale).	• Nausea (54.9%) • Alopecia (51.0%) • Anorexia (43.1%) • Vomiting (41.2%) • Taste alteration (39.2%) • Diarrhea (23.5%) • Constipation (13.7%) • Tinnitus (9.8%) • Hypocalcemia (3.9%) • Dizziness (3.9%) • Headache (2.0%) • Salivation (2.0%)
(9)	Prospective (78)	Cisplatin, carboplatin, and oxaliplatin.	• 64.6% reactions were possible, followed by category probable with frequency 35.4%, and there were no certain reactions (WHO assessment scale). • 59.4% ADRs were possible and 40.6% were probable (Naranjo's algorithm)	• 12.5% ADRs were of less severity categorized as mild, 68.75% were moderate and 18.75% ADRs were categorized as severe (Hartwig and Siegel scale)	• 47.9% ADRs were definitely preventable, 15.6% were probably preventable and 35.6% ADRs were not preventable (modified Schumock and Thornton scale)	• Vomiting (46%) • Diarrhea (15%) • Abnormal renal (8%) • Constipation (7%) • Myelosuppression (5%) • Anemia (5%) • Thrombocytopenia (5%) • Alopecia (5%)
(6)	Prospective, observational noninterventional study (140)	Cisplatin, carboplatin, and oxaliplatin	• 74.29% ADRs were possible, followed by 25.71% probable (WHO assessment scale).	• Most of ADRs were of mild nature (90.71%) followed by moderate (9.29%), no case of severe category (Hartwig and Siegel scale).	• 97.14% of cases of ADRs were of predictable and 2.86% ADRs were not predictable (Council for International Organization of Medical Sciences (CIOMS))	• Vomiting (19.28%) • Alopecia (12.85%) • Diarrhea (10.71%) • Anorexia (10.71%) • Pigmentation of the nail (7.14%) • Constipation (6.42%) • Decrease Hb (5%) • Nausea (3.57%) • Nervousness (3.57%) • Headache (3.57%) • Dizziness (2.14 %) • Mucositis (2.14%)

Predictability assessment

The predictability assessment conducted with the Council for International Organization of Medical Sciences (CIOMS). 97.14% of cases of ADRs were predictable and 2.86% ADRs were not predictable (6). Two articles did not use predictability assessment (9,10) (Table 1).

DISCUSSION

The aim is to identify adverse drug reactions of the platinum agent and identify the assessment of platinum adverse drug reactions. Because ADRs assessment is important to reduce patient suffering and help healthcare professionals in planning appropriate treatment. The databases that we use are PubMed, ScienceDirect, and Google Scholar. We use that database because it provides free articles. Our study reviewed 15 articles (total of 474 articles) assessed platinum adverse drug reactions. Finally, it is only 3 articles that we're including with our study. All of these studies used a prospective study (6,9,10). One article used a prospective observational noninterventional study (6). According to one research, prospective studies have higher accuracy and higher efficiency (11).

From all of those articles, 61.24% reported that platinum ADRs occurred in women and the rest occurred in men (38.75%). Women may be more susceptible to ADRs than men, This increased susceptibility in women is thought to be due to their longer QTc interval compared with men (7) . Patients with the age group above 41 years are more susceptible to ADRs. This is in agreement with the study conducted by Belachew (2016) where he has stated that the majority of patients who experienced ADRs were 41-50 years old (12). Platinum analog is clinically used for a variety of malignancies including ovarian carcinoma, lung cancer, carcinoma cervix, carcinoma colon, and others. The use of platinum analog for various malignancies because platinum has a cytotoxic effect in all stages of the cell and binds the DNA (13).

The most common ADRs from platinum analog is vomiting (35.49%) followed by alopecia (22.95 %), nausea (19.4%), anorexia, diarrhea, taste alteration, constipation, tinnitus, abnormal renal, and dizziness. All the articles reported that platinum compounds have a high potential to cause various adverse drug reactions in cancer patients (6,9,10). Vomiting is the most common adverse effects in 3 platinum analog, especially cisplatin (75% -100%) and carboplatin (65% - 81%) (14) . Some literature presents that platinum analog with a high emetogenic effect is cisplatin (5,15) . Severe nausea may be seen with carboplatin and oxaliplatin better than cisplatin (5). Alopecia often occurs in patients using platinum, it is because hair follicles comprise a fast-growing cell, which means the chemotherapy drugs can result in the loss of hair (16).

The platinum analog that uses in this study is cisplatin, carboplatin, and oxaliplatin. There are currently three platinum analogs used in clinical practice: cisplatin, carboplatin, and oxaliplatin (13). Several platinum analogs are marketed in one country, among them are nedaplatin in Japan, nedaplatin in Korea, and lobaplatin in China (5).

Naranjo's algorithm is one of the most commonly used and accepted in causality assessment (1,7). The result from 3 articles used assessment with the WHO assessment scale, the median of all articles are present 69.29% ADRs is possible. Possible mean reasonable temporal relationship, but could be explained by concurrent disease or drugs, no information on withdrawal (2). Average that is probable (reasonable temporal relationship, unlikely to b attributed to diseases processes or other drugs with reasonable dechallenge response) 30.7%. assessment with Naranjo's algorithm, 60.7 % ADRs was possible and 39.3 % were probable. Assessment with WHO the result of the assessment is more likely to be possible than probable. In contrast with Naranjo's algorithm, the result is more likely to be probable than possible, but from both of these causality assessments, we can see the result obtained from the two assessments are not too different.

All studies used Hartwig and Siegel scale to assess the severity. Three studies categorized ADRs were mild, three studies were moderate (6,9,10) and only one study was severe (9). It means most ADRs from platinum analogs are more mild and moderate.

Preventability used modified Schumock and Thornton scale, it got 47.9% ADRs were definitely preventable, 15.6% were probably preventable and 35.6% ADRs were not preventable (6,9,10). Most of the ADRs were definitely preventable, but many ADRs are also categorized as not preventable. It is only a study that assessed predictability, The predictability assessment that conducted with CIOMS,. 97.14% of ADRs cases were predictable and 2.86% ADRs were not predictable (6). it is mean that we have to monitor ADRs to patients because there are ADRs that are not predictable even though a little.

CONCLUSION

Our review of ADRs associated with platinum analogs indicates the most common ADRs are vomiting, followed by alopecia, nausea, anorexia, diarrhea, taste alteration, constipation, tinnitus, abnormal renal, and dizziness. Most ADRs are possible than probable. Most ADRs of platinum analogs are moderately followed by mild and severe. The preventability assessment of platinum analogs, most of all definitely preventable followed by not preventable and probably preventable. Almost all ADRs of platinum are predictable. Currently, there is a lack of information on platinum ADRs. In the interest of patient safety, sufficiently large prospective studies should be considered to clarify this issue.

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