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CLINICAL & BASIC RESEARCH

Predictors of Hypersensitivity Reactions to Platinum-Based Chemotherapy in a Tertiary Care Hospital in Oman

A case control study

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abstract: ***Objectives:*** This study aimed to estimate the prevalence and evaluate risk factors of hypersensitivity reactions (HSRs) to platinum-based compounds (PBCs) in cancer patients. PBCs play an important role in cancer therapy. However, one of the drawbacks of PBCs is the occasional occurrence of HSRs, which can lead to serious consequences. ***Methods:*** This retrospective case control study was conducted from January 2013 to December 2020 at Sultan Qaboos University Hospital, Muscat, Oman and included patients who received any PBC for the management of non-haematological cancers. Data regarding demographic characteristics and diseases and treatment details were collected from the hospital's electronic database. The data were quantitatively described and Student's t-test and Wilcoxon Mann-Whitney tests were used to detect significant differences. ***Results:*** A total of 38 cases and 148 matched controls were studied. The prevalence of HSRs to PBCs in the cohort of this study was 4.7% (95% confidence interval: 3.33–6.37%), higher with carboplatin compared with cisplatin and oxaliplatin. The female gender (P = 0.032), concomitant taxanes (P = 0.002) and concurrent radiation (P <0.001) were significant predictors of HSRs to PBCs. The majority of the reactions were of mild to moderate severity, and the rechallenge rate after HSR development was 13%. ***Conclusion:*** HSRs to PBCs impact therapy decisions and understanding the risk factors is important to improve treatment outcomes in cancer patients.

Keywords: Anti-neoplastic Agent; Hypersensitivity; Medical Oncology; Platinum; Oman.

Advances in Knowledge

- *This is the first report from a Middle Eastern country reporting on the incidence, presentation, outcomes and predictive factors of hypersensitivity reactions (HSRs) to platinum-based compounds (PBCs).*

Applications to Patient Care

- *This study showed that approximately 5% of patients can develop HSRs to PBCs, and the combination of platinum–taxane in addition to concurrent chemo-radiation significantly predicted higher HSR rates, this should be taken into consideration during treatment planning.*
- *As most HSRs were of a lower grade, further studies should be conducted on challenge criteria and protocols, so as to not compromise treatment outcomes caused by the elimination of platinum use in patients showing mild signs of HSR.*

Platinum-based compounds (PBCs; e.g. cisplatin, carboplatin, oxaliplatin) play a very important role in cancer therapy. They act by inhibiting DNA replication through the formation of DNA adducts leading to apoptosis and thus prevent replication of cancer cells.[1] These compounds have been approved for treatment of several cancers of different origins. For several cancers, PBCs form the backbone of treatment.[2] However, one of the drawbacks of PBCs is the occasional occurrence of hypersensitivity reaction (HSR), which can be potentially fatal. The incidence of HSRs to PBCs is rising due to the growing use of these agents in cancer management.[2] The symptoms of HSRs range from a mild skin rash to severe anaphylaxis, and multiple types of hypersensitivity pathways seem to be implicated.[2,3]

The reported incidence of HSRs to PBCs differs according to the specific agent used, ranging from 5–20% for cisplatin, depending on the concomitant therapy.[4] For carboplatin, HSR occurs at a rate <1% during the first five cycles, with a sharp increase to 44% in the third-line treatment setting, after more than eight cycles have been administered.[5] Oxaliplatin-related HSR has been reported to be less common, but with the growing use of this drug, the frequency ranges from 3.6–18.9% in clinical practice.[2,3]

The risk of HSRs to both cisplatin and carboplatin increases with the increase in the number of infusions

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and the cumulative dose delivered, as well as the type of concomitantly administered antineoplastic drugs.[2] HSRs to cisplatin also increase with concurrent radiation therapy.[4] Patients who receive first-line platinum-based chemotherapy and are then treated again with a platinum agent at the time of relapse are at the greatest risk of experiencing HSRs after a long platinum-free interval.[6] Other factors such as higher lymphocyte and neutrophil count and lower monocyte count are also considered potential risk factors.[7,8]

The occurrence of HSRs raises important issues when it comes to subsequent therapy decisions, because changing the chemotherapy could affect the tumour's evolution. Though the characteristics of platinum-based HSRs are widely reported, limited data are available regarding such reactions in different types of patients. Additionally, to the best of the authors' knowledge, HSRs to PBCs have not been previously studied in the Omani population and ethnic variations could play an important role in determining such outcomes. Therefore, this study aimed to estimate the prevalence of HSRs and evaluate the predictive factors for the occurrence of allergic reactions to PBCs in cancer patients treated at a tertiary care hospital in Oman.

Methods

This retrospective case control study included patients who had received any platinum-based chemotherapy regimen for the treatment of non-haematological tumours at the Sultan Qaboos University Hospital (SQUH), a tertiary care and cancer centre in Muscat, Oman, between January 2013 and December 2020. Adult cancer patients, who had received at least one dose of a platinum agent during this period were included. Details of chemotherapy were retrieved from the Cytosoft© software (Guava Technologies, Inc., Hayward, California, USA) used for chemotherapy order management. Chemotherapy protocols at the authors' institution are based on British Columbia Cancer Agency protocols. All patients had received dexamethasone and an antihistamine prior to every dose of platinum chemotherapy as part of the routine supportive care protocol.

Data on HSRs were collected from either the adverse drug reaction form or the electronic patient's record (EPR). This reporting system can be activated by the physician, the pharmacist or the nurse involved in the patient care and sent to a central pharmacovigilance centre. Only patients with acute infusion-related HSRs were included in the study.

The HSR severity was defined according to the Common Terminology Criteria for Adverse Events Version 4. For each case, four controls were selected. Controls were randomly selected patients who received platinum-based chemotherapy and did not develop symptoms of HSRs; they were stratified according to age, gender and the year of treatment. Approximately 18–20 random patients, with males and females in equal numbers, were selected from each treatment year within the study period. The controls for disease site or chemotherapeutic regimens were not matched.

Patient data were collected from the EPR, including demographic characteristics (age, gender, height, weight, diagnosis and stage of the disease), history of allergy to other medications, baseline laboratory parameters (complete blood count including haemoglobin, white blood cell with differentials, platelet count) and treatment details (type of platinum agent used, treatment setting, number of cycles received prior to the development of HSR, cumulative dose received prior to HSR, grade of HSR, platinum-free interval, concomitant chemotherapy, concomitant radiotherapy and subsequent therapy after occurrence of HSR).

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between the groups were analysed using Pearson's χ^2 tests (or Fisher's exact tests for expected cells <5). For continuous variables, mean and standard deviations were used and differences between the groups stratified by platinum-based HSRs were analysed using Student's t-test. Variables that were not normally distributed (e.g. number of cycles, cumulative dose) were summarised using median and interquartile range and the analysis was performed using the Wilcoxon-Mann-Whitney test. The Kolmogorov–Smirnov test was used to determine normal distribution. Odds ratios (OR) with their respective 95% confidence intervals (CIs) were derived using the univariate logistic regression model. An a priori two-tailed level of significance was set at 0.05. Statistical analyses were conducted using STATA, Version 13.1 (STATA Corporation, College Station, Texas, USA).

Ethical approval of the study was granted by the Medical Research Ethics Committee at SQU College of Medicine and Health Sciences (MREC # 2478).

Results

A total of 812 patients received PBCs of which there were 38 cases of HSRs (20 for carboplatin, 13 for oxaliplatin and five for cisplatin). The incidence of HSRs in patients receiving PBCs was 4.7%. All cases developed an immediate allergic reaction to a platinum-based drug during infusion and up to one hour later.

Clinical features of allergy ranged from a mild skin rash to more severe bronchospasm and tachycardia. A total of 186 patients including cases (n = 38) and case-matched controls (n = 148) were studied for predictive factors. Of the cohort, 88 (47.3%), 89 (47.8%) and 37 (19.9%) patients received carboplatin, oxaliplatin and cisplatin, respectively, whereas four patients (2.2%) received all three types of platinum compounds, and 21 patients (11.3%) received at least two platinum compounds before the occurrence of HSR.

The mean age of the cohort was 52.6 ± 15.7 years, and 53.2% of the cohort were female. No significant difference in age was noted between the cases and the controls (51.6 versus 52.8 years; P = 0.704); however, females were significantly more likely than males to be associated with HSR reactions (68.4% versus 49.3%; P = 0.032). In addition, a trend of a higher HSR rate with a lower body surface area was observed between the controls and cases (1.67 versus 1.59 m^2; P = 0.064). No significant differences were observed in other demographic features, clinical stage, blood counts and prior exposure to platinum compounds between the cases and controls [Table 1].

The majority of the patients were treated for stage IV disease (67.7%). Consequently, 67.7% of the patients received palliative chemotherapy, whereas 15.1% and 17.2% of the patients received neoadjuvant and adjuvant chemotherapy, respectively. The most frequently used concomitant chemotherapeutic agents were paclitaxel, gemcitabine and 5-fluorouracil. Concurrent radiation was used in 28 (15.1%) patients [Table 2].

Patients who developed a reaction to carboplatin had a median number of five (range: 2–8) cycles prior to the HSRs, compared with a median of three cycles (range: 1–6) for cisplatin and eight (range: 7–10) cycles for oxaliplatin. Only three out of 38 patients developed an HSR with the first dose of a platinum agent. The cumulative number of cycles of any platinum received by the patient was not a significant predictor for an HSR, with an average of nine cycles in each group (P = 0.431). The average cumulative total dose of carboplatin, cisplatin and oxaliplatin prior to an HSR was 3,362 mg, 3,449 mg and 1,699 mg, respectively.

A higher rate of HSR was observed with the concomitant use of taxane chemotherapy and concurrent chemoradiation. A taxane was administered concomitantly with a platinum in 42 patients in the entire cohort. Out of the 38 cases, 16 developed HSR (42.1%, 95% CI: 26–59%), compared to 26 out of 148 controls (17.6%, 95% CI: 12–25%; P = 0.002). The use of a taxane was significantly associated with the development of HSR to platinum-based

Table 1: Characteristics of included patients on platinum-based chemotherapy (N = 186)

Characteristic	n (%)			*P* value
	All (N = 186)	Controls (n = 148)	Cases (n = 38)	
Mean age in years ± SD	52.6 ± 15.7	52.8 ± 15.7	51.6 ± 15.9	0.704
Gender				
Female	99 (53.2)	73 (49.3)	26 (68.4)	0.032
Male	87 (46.8)	75 (50.7)	12 (31.6)	
Mean BSA in m^2 ± SD	1.65 ± 0.24	1.67 ± 0.24	1.59 ± 0.26	0.064
Mean BMI in kg/m^2 ± SD	25.07 ± 8.64	23.53 ± 6.57	25.46 ± 9.07	0.218
Diagnosis				
Lower GIT	70 (37.6)	58 (39.2)	12 (31.6)	-
Gynaecological	24 (12.9)	16 (10.8)	8 (21.1)	-
Breast	24 (12.9)	18 (12.2)	6 (15.8)	-
Upper GIT	22 (11.8)	16 (10.8)	6 (15.8)	-
Lung	18 (9.7)	17 (11.5)	1 (2.6)	-
Urological	15 (8.1)	14 (9.5)	1 (2.6)	-
Head and neck	8 (4.3)	5 (3.4)	3 (7.9)	-
Skin	3 (1.6)	2 (1.4)	1 (2.6)	-
Bone	2 (1.1)	2 (1.4)	0 (0.0)	-
Concurrent chemotherapy type				
5-FU-based	77 (41.4)	65 (43.9)	12 (31.6)	0.168
Paclitaxel	42 (22.6)	26 (17.6)	16 (42.1)	0.001
Gemcitabine	39 (21.0)	30 (20.3)	9 (23.7)	0.645
Etoposide	17 (9.1)	17 (11.5)	0 (0.0)	0.026
Pemetrexed	6 (3.2)	5 (3.4)	1 (2.6)	1.000
Capecitabine	3 (1.6)	3 (2.0)	0 (0.0)	1.000
Doxorubicin/epirubicin	2 (1.1)	2 (1.4)	0 (0.0)	1.000
Mean baseline blood count ± SD				
Hb in g/dL	11.1 ± 1.7	12.0 ± 1.8	10.9 ± 1.7	0.487
WBC × 10^3/L	6.6 ± 2.9	6.6 ± 3.0	6.5 ± 2.5	0.912
ANC × 10^3/L	4.3 ± 4.8	4.1 ± 4.3	4.9 ± 6.4	0.372
Eosinophils × 10^3/L	0.29 ± 0.70	0.32 ± 0.77	0.19 ± 0.20	0.291
Monocytes × 10^3/L	0.64 ± 0.55	0.67 ± 0.6	0.53 ± 0.26	0.204
ALC × 10^3/L	2.07 ± 1.6	1.99 ± 1.01	2.3 ± 2.8	0.21
PLT × 10^3/L	339 ± 144	336 ± 151	350 ± 118	0.594
Allergy to other medications	10 (5.4)	7 (4.7)	3 (7.9)	0.427

SD = standard deviation; BSA = body surface area; BMI = body mass index; GIT = gastrointestinal tract; 5-FU = 5-fluorouracil; Hb = haemoglobin; WBC = white blood cell; ANC = absolute neutrophil count; ALC = absolute lymphocytes count; PLT = platelets.

Table 2: Predictors associated with hypersensitivity reaction

Characteristic	n (%)			*P* value
	All (N = 186)	Controls (n = 148)	Cases (n = 38)	
Disease stage				
I	5 (2.7)	3 (2.0)	2 (5.3)	0.557
II	18 (9.7)	15 (10.1)	3 (7.9)	
III	37 (19.9)	31 (20.9)	6 (15.8)	
IV	126 (67.7)	99 (66.9)	27 (71.1)	
Previous lines of therapy				
Neoadjuvant	28 (15.1)	21 (14.2)	7 (18.4)	0.441
Adjuvant	32 (17.2)	28 (18.9)	4 (10.5)	
Palliative	126 (67.7)	99 (66.9)	27 (71.1)	
Previous exposure to platinum	20 (10.8)	16 (10.8)	4 (10.5)	1.000
Median number of cycles (IQR)	9 (6–12)	9 (6–12)	8 (5–12)	0.431
Median cumulative dose in mg (IQR)	1,890 (1,200–3,684)	1,800 (1,174–3,615)	2,075 (1,352–3,795)	0.446
Concomitant taxane therapy	42 (22.6)	26 (17.6)	16 (42.1)	0.002
Concomitant radiotherapy	28 (15.1)	15 (10.1)	13 (34.2)	<0.001

IQR = interquartile range.

Table 3: Hypersensitivity reaction grade according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4 (N = 38)

Grade of HSR	n (%)
I	15 (39.5)
II	15 (39.5)
III	8 (21.1)
IV	0 (0.0)

HSR = hypersensitivity reaction.

agents (OR = 3.4, 95% CI: 1.6–7.4; *P* = 0.002). Likewise, of the 28 patients who received concurrent radiation, 13 out of 38 cases (34.2%) and 15 out of 148 controls (10.1%) developed HSR (OR = 4.8, 95% CI: 2.1–11.4; *P* <0.001).

Eight patients developed grade III HSR and no patient developed a grade IV reaction. After the onset of an allergic episode, the platinum agent was permanently discontinued in 33 (86.8%) patients. Two patients received the same agent successfully at a slower rate and three patients with an HSR to carboplatin were shifted to cisplatin. Out of the three, only one showed cross-reactivity. All patients who received a platinum agent after a documented HSR had grade I–II HSRs initially, mainly manifesting as itching, urticaria and erythema within a few minutes of administration [Table 3].

Discussion

To the best of the authors' knowledge, this is the first report from a Middle Eastern country on the incidence, presentation, outcomes and predictive factors of HSRs to PBCs. Over a period of eight years, the incidence of HSR was 4.7%; it was higher with carboplatin compared with either cisplatin or oxaliplatin. Patients receiving a taxane or radiotherapy concomitantly were at a significantly higher risk of developing an HSR. Although the majority of the patients developed either grade I or II HSR, a platinum compound of any kind was omitted from the chemotherapy combination for the subsequent cycles.

The widespread use of PBCs in the last decade has contributed significantly to HSR development in the treatment of cancer patients. In the literature, varying HSR rates between different platinum-based agents have been reported.[2] The results of the current study are consistent with the published data, suggesting that HSRs are characteristically uncommon in the first few cycles of treatment with PBCs.[2,3] For carboplatin, the incidence was reported to be as low as 1% in the first five cycles with an exponential surge up to 6.5% during the sixth cycle and up to 27% in patients who received seven or more cycles.[2,9,10] At the authors' institution, patients taking carboplatin had a cumulative rate of HSR of 22.7%, higher than the rate of HSRs with cisplatin or oxaliplatin. Carboplatin hypersensitivity occurred after a median of five cycles, which is considered borderline in other reports.[2] The rate of cisplatin hypersensitivity was 14.6%, and the occurrence of HSRs was evident between the first and the sixth cycles (median = 3), which is earlier than the 4–8th cycle mark.[2] On the other hand, oxaliplatin HSR was found to manifest after a median of eight cycles, which is significantly later than a median of three cycles.[11] These discrepancies in the characteristics of HSR between different populations warrant further investigations. HSRs may happen in association with multiple factors such as gender, concomitant chemotherapy and radiation therapy.

Only a few studies have investigated the association between HSRs occurring in different

genders. Shibata *et al*. reported that there was no interrelation between HSRs and gender;[12] while Seki *et al*. suggested that young female patients were more prone to experiencing HSRs when compared with males of the same age.[8] The analysis in this study showed that females were significantly more likely to develop HSRs than males (68.4% versus 49.3%; $P = 0.032$); the reason for this prevalence is unknown. However, some investigators proposed that hormonal influences play a significant role in developing HSRs, as well as the presence of pre-existing allergies to food, drugs and allergens.[13] Patients who were treated at the authors' hospital were asked about any known allergies to food, drugs as well as other allergens. However, the low level of awareness of patients regarding their pre-existing allergies cannot be ruled out.

The concomitant use of other antineoplastic drugs has been reported to increase the rate of HSRs in cancer patients, especially when carboplatin is used concomitantly with paclitaxel.[2] The data in this study showed that the incidence of HSRs when using concurrent paclitaxel was significantly higher when compared with other antineoplastics, such as gemcitabine and 5-fluorouracil-based chemotherapies. Studies suggest that other chemotherapeutic agents should be used to avoid this interaction. For example, pegylated liposomal doxorubicin (PLD) was studied, which demonstrated a lower incidence of HSR when compared with paclitaxel, where the combination of carboplatin–paclitaxel versus carboplatin–PLD was associated with a risk of 18.8% and 5.6% of HSR occurrence, respectively.[14]

As studies have reported, the patho-physiology of HSRs to PBCs is not limited to type I HSR,[2,3] and this might overlap with the mechanism of HSR to taxanes, which is probably not immunoglobulin E mediated.[15] However, in clinical practice the features of HSRs to PBCs and taxanes are distinct, and clinicians are less likely to misclassify the cause of HSRs.[15] Concomitant use of radiation therapy might also be considered a predictor for HSRs. In this study, a significant association was found (34.2%; $P < 0.001$). This observation is consistent with multiple reports that have suggested the occurrence of HSRs when using PBCs followed by radiation therapy.[4] This might be related to the antigen release of cytokine release caused by irradiation and caution is warranted in this group of patients.[4,16]

Approximately 80% of the HSRs seen in this study were grades I and II. However, platinum chemotherapy was permanently discontinued in 90% of the cases. Out of the five patients who were rechallenged, four were able to successfully receive the same or a different platinum agent without untoward reactions; one patient showed cross-reactivity with another platinum agent. This rate of rechallenge was very low. Tate *et al*. demonstrated the safety of changing the platinum compound with a low risk of HSR recurrence.[17] In addition, slowing the infusion rate was found to allow successful delivery of the platinum agents in 97% of 174 patients with platinum HSR.[18] Furthermore, skin testing, despite its limited use, was shown to have a high level of accuracy of detecting an HSR (81–88%);[19,20] these management lines should be considered to allow those patients at high risk to receive a safe course of treatment without compromising in efficacy.

This study was subject to certain limitations, such as the case-control design with inherent selection bias risk and the long period of time taken to accumulate the data. However, this is due to the rarity of HSR events. In addition, the fact that physicians, pharmacists and nurses can enter information in either hard or soft copy reduces the chances of underreporting.

Conclusion

HSRs to platinum agents are common but fortunately, most patients experience mild reactions. Predicting the risk depends on multiple factors, and that can be used to monitor future patients to prevent unwanted HSRs. Further studies may help elucidate the interactions and dynamics of HSRs with other chemotherapeutic agents and radiation therapy.

AUTHORS' CONTRIBUTION

MM conceptualised the idea of the study and BS managed the project. KB designed the study. FR, BA and KM collected the data. EA conducted the literature review and structured the study background. BS, FR and NW analysed and interpreted the data. IZ conducted the statistical analysis. BS and NW drafted the manuscript. KB, IB and KM reviewed and edited the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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