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

A case-control study

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Abstract

Objectives: Platinum-based compounds (PBC) play an important role in cancer therapy. However, one of the drawbacks of PBC is the occasional occurrence of hypersensitivity reactions (HSR) which can lead to serious consequences. The aim of the study is to estimate the prevalence and evaluate risk factors of HSR to PBC in cancer patients. ***Methods:*** A case-control study of patients who received any PBC for the management of non-haematological cancers from 2013 to 2020 at Sultan Qaboos University Hospital, Oman. Data regarding demographic features and diseases and treatment details were collected from the hospital's electronic patients record. We quantitatively described the data, and Student's t-test and Wilcoxon Man-Whittney

tests were used to detect significant differences. ***Results:*** A total of 38 cases and 148 matched controls were studied. The prevalence of HSR to PBC in our cohort was 4.7% (95% confidence interval: 3.33%-6.37%), more with carboplatin compared to cisplatin and oxaliplatin. In our study, female gender (p=0.032), concomitant taxanes (p=0.002) and concurrent radiation (p<0.001) were significant predictors of HSR to PBC. The majority of reactions were of mild to moderate severity and the rechallenge rate after HSR development was 13%. ***Conclusion:*** HSR to PBC impact therapy decisions and understanding the risk factors are important to improve treatment outcomes in cancer patients.

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

Advances in Knowledge

- This is the first report from the middle-eastern countries reporting the incidence, presentation, outcomes and predictive factors of HSR to PBC.

Application to Patient Care

- As the study showed that around 5% of patients can develop HSR to PBC, 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.

- Also, since most of the reactions were of a lower grade, more work should be done on re-challenge criteria and protocols, as not to compromise treatment outcomes caused by the elimination of platinum use in patients showing mild signs of HSR.

Introduction

Platinum-based compounds (PBCs) (cisplatin, carboplatin, oxaliplatin) play a very important role in cancer therapy. They act by inhibition of DNA replication through the formation of DNA adducts leading to apoptosis, and hence preventing 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 reactions (HSR) which can be potentially fatal. The incidence of HSR to PBC is rising due to the growing use of these agents in cancer

management.[2] The symptoms of HSR 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 HSR to PBC differs according to the specific agent used, ranging from 5% to 20% with cisplatin, depending on concomitant therapy.[4] For carboplatin, HSR occurs at a rate of < 1% during the first five cycles, with a sharp increment 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 HSR to both cisplatin and carboplatin increase with increasing number of infusions and the cumulative dose delivered, as well as the type of concomitantly administered antineoplastic drugs.[2] Cisplatin HSRs 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 HSR after a long platinum-free interval.[6] Other factors such as higher lymphocyte and neutrophil count and lower monocyte count are also implicated as potential risk factors.[7,8]

The occurrence of HSR 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 HSR are widely reported, limited data are available regarding such reactions in different types of patients. Additionally, to the best of our knowledge, HSR to PBC has not been previously studied in the Omani population and ethnic variations can play an important role in determining such outcomes. Therefore, the aim of this study was to estimate the prevalence of HSR and to evaluate the predictive factors for the occurrence of allergic reactions to PBC in cancer patients treated at a tertiary care centre in Oman.

Methods

In this case-control study, we included patients who received any platinum-based chemotherapy regimen for the treatment of non-hematological tumors at the Sultan Qaboos University Hospital (SQUH), a tertiary care and cancer center in Oman, between January 2013 and December 2020.

The study included adult cancer patients, who received at least one dose of a platinum-agent during this period. Details of chemotherapy were retrieved from the Cytosoft© software used for chemotherapy order management. Chemotherapy protocols at our institution are based on British Columbia Cancer Agency (BCCA) protocols. Ethical approval of the study was granted by the Medical Research Ethics Committee at SQU College of Medicine and Health Sciences. All patients had received dexamethasone and an antihistamine prior to every dose of platinum chemotherapy as part of the routine supportive care protocol.

HSRs were reported either using the adverse drug reaction form or were documented in the electronic patient's record (EPR). This reporting system can be activated either by the physician, the pharmacist or the nurse involved in the patient care and sent to a central pharmacovigilance centre. Only patients with acute HSR infusion-related reactions were included in the study. HSR severity was defined according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE ver.4). For each case, four controls were selected. Controls were randomly selected patients who received platinum –based chemotherapy and did not develop symptoms of HSR, and were stratified according to age, gender, and the year of treatment. About 18-20 random patients with equal numbers of males and females were selected from each treatment year within the study period. We did not match the controls for disease site or chemotherapeutic regimens.

Patient data were collected from the EPR and included demographic features (age, gender, height, weight, diagnosis, and stage of the disease), history of allergy to other medications, baseline laboratory parameters (complete blood count including hemoglobin, white blood cell with differentials, platelets count), and treatment details (type of platinum agent used, treatment setting, number of cycles received prior to the development of HRS, cumulative dose received prior to HRS, grade of HSR, platinum-free interval, concomitant chemotherapy, and 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 groups were analysed using Pearson's $\chi 2$ tests (or Fisher's exact tests for expected cells <5). For continuous variables, mean and standard

deviation were used to summarize the data and differences between groups stratified by platinum-based hypersensitivity reactions were analysed using Student's t-test. Variables that were not normally distributed (e.g., number of cycles, cumulative dose) were summarized using median and interquartile range (IQR) and analysis was performed using Wilcoxon-Mann-Whitney test. The Kolmogorov–Smirnov test was used to determine normal distribution. Odds ratios (OR) with their respective 95% confidence intervals (CI) were derived using 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, TX, USA).

Results

Between 2013 and 2020, a total of 812 patients received PBC at our institution. A total of 38 cases of HSR were reported (Carboplatin; 20, Oxaliplatin; 13 and Cisplatin; 5). The incidence of HSR in patients receiving PBC was 4.7% (38/812). 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 mild skin rash to more severe bronchospasm and tachycardia. 148 case matched controls were identified and a total of 186 patients including cases and controls were studied for predictive factors. Of the cohort, 88, 89, and 37 patients received carboplatin, oxaliplatin and cisplatin, respectively, whereas four patients (2%) received all three types of platinum compounds, and 21 patients received to at least two platinum compounds before the occurrence of HSR.

The mean age of the cohort was 53 ± 15 years and 53% (99/187) were females. The demographic and clinical characteristics of the study population are shown in **Table 1**. The majority of patients were treated for stage IV disease (68%). Details of clinical stage at the time of allergic reaction are shown in **Table 2**. Consequently, 68% of the patients were receiving palliative chemotherapy, whereas 15 and 17% of the patients were receiving 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%) patients.

No significant difference in age was noted between the cases and controls (52 *vs* 53 years; p = 0.615), however, females were significantly more likely to be associated with HSR reactions than males (26% *vs* 14%; p = 0.032). In addition, a trend towards higher HSR rate with a lower body surface area was observed (1.67 *vs* 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 cases and controls.

Patients who developed a reaction to carboplatin, had a median number of 5 (2-8) cycles prior to the HSR, compared to a median of 3 cycles (1-6) for cisplatin, and 8 (7-10) cycles for oxaliplatin. Only 3/38 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 HSR, with an average of nine cycles in each group (p = 0.4). The average cumulative total dose of carboplatin, cisplatin and oxaliplatin prior to HSR was 3362, 3449 and 1699mg, respectively.

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 during the entire cohort. Out of the 38 cases, 16 developed HSR (42%; 95% CI: 26%-59%), compared to 26/148 (18%; 95% CI: 12%-25%) controls (p = 0.002). Use of a taxane was significantly associated with the development of HSR to platinum-based agents (odds ratio (OR), 3.4; 95% CI: 1.6–7.4; p = 0.002). Likewise, of the 28 patients who received concurrent radiation, 13/38 cases (35%), and 15/148 controls (10%) developed HSR (OR, 4.8 95% CI: 2.1–11.4; p < 0.001).

The grade of HSR according to NCI-CTCAE v4.0 is shown in Table 3. Eight patients developed grade III HSR, and no patient developed grade IV reaction. After the onset of allergic episode, the platinum agent was permanently discontinued in 33 (87%) 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 to II HSRs initially, mainly manifesting as itching, urticaria and erythema within few minutes of administration.

Discussion

To the best of our knowledge, this is the first report from the middle-eastern countries reporting the incidence, presentation, outcomes and predictive factors of HSR to PBC. Over a period of eight years, the incidence of HSR was 4.7%, more with carboplatin compared to 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 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 broad use of PBC in the last decade has contributed significantly to HSR development in the treatment of cancer patients. In literature, varying HSR rates between different platinum-based agents have been reported.[2] Our results are consistent with the published data suggesting that HSRs are characteristically uncommon in the first few cycles of treatment with PBC. [2,3] For carboplatin, the incidence has reported to be as low as 1% in the first 5 cycles[2] with an exponential surge to 6.5% during the 6th cycle[9] and up to 27% in patients who received seven or more cycles.[10] At our institution patients taking carboplatin had a cumulative rate of HSR of 23%, higher than the rate of HSRs with cisplatin or oxaliplatin. Carboplatin hypersensitivity occurred after a median of 5 cycles, which is considered borderline in other reports.[2] The rate of cisplatin-hypersensitivity was 14% and the occurrence of HSRs was evident between the 1st and the 6th cycle (median=3) which is earlier than the 4th – 8th cycle mark.[2] On the other hand, oxaliplatin HSR was found to manifest after a median of 8 cycles, which is significantly later than a median of 3 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 investigated the association between HSRs occurrence in different genders. Shibata et al.[12] reported that there was no interrelation between HSRs and gender, while Seki et al.[8] suggested that young female patients were more prone to experience HSRs when compared to males of the same age. Our analysis showed that females were significantly more likely to develop HSRs than males (26% *vs* 14%; 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 preexisting allergies to food, drugs and allergens.[13] Patients who were treated at our hospital were asked regarding the presence of allergies towards food, drugs as well as other allergens. However, low level of awareness by patients regarding their preexisting allergies cannot be excluded.

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] Our data showed that the incidence of HSRs when using concurrent paclitaxel was significantly higher when compared with other antineoplastics, such as, gemcitabine and 5-fluorouracil (5-FU) based chemotherapies. Studies suggest the use of other chemotherapeutic agents to avoid this interaction. For example, pegylated liposomal doxorubicin (PLD) was studied and demonstrated a lower incidence of HSR when compared to paclitaxel, where a combination of carboplatin-paclitaxel vs carboplatin-PLD was associated with 18.8% and 5.6% risk of HSR occurrence, respectively.[14]

As studies have reported, the patho-physiology of HSR to PBC is not limited to type I HSR[2,3] and this might overlap with the mechanism of HSR to taxanes which is probably not IgE mediated.[15] However, in clinical practice the features of HSR to PBC and taxanes are distinct, and clinicians are less likely to misclassify the cause of HSR.[15] Concomitant use of radiation therapy might also be considered predictor for HSR. In our study, a significant association was found (35%; $p<0.001$). This observation Is consistent with multiple reports which have suggested the occurrence of HSR when using PBC followed by radiation therapy.[4] This might be related to the either antigen release of cytokine release caused by irradiation and caution is warranted in this group of patients.[4,16]

Around 80% of the HSR seen in our study were grade I/II. However, platinum chemotherapy was permanently discontinued in 90% of the cases. Out of the five patients who were re-challenged, four were able to successfully receive the same or a different platinum agent without untoward reactions, and 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 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 limited use, was shown to have a high level of accuracy of detecting a HSR (81% to 88%)[19,20] and these management lines should be considered to allow those patients at high risk to receive a safe course of treatment without efficacy compromise. There are limitations of the study, such as the case-control design with inherent selection bias risk and long period of time to accumulate the data. However, this is due to the rarity of HSR events. Also, the fact that physicians, pharmacists and nurses can enter information either in hard or soft copy reduces the chances of underreporting.

Conclusion

In conclusion, HSR to platinum agents are not uncommon. Fortunately, most patients experience mild reactions. Predicting the risk depends on multiple factors, and that can be used to monitor future patients to prevent from unwanted HSR. Also, further studies may help elucidate the interactions and dynamics of HSR with other chemotherapeutic agents and radiation therapy.

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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 conflicts of interest.

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Table 1: Demographic and clinical characteristics.

Characteristic, n (%) unless specified otherwise	**All (N = 186)**	**Controls (n = 148)**	**Cases (n = 38)**	***P* value**
Age, mean ± SD, years	52.6 ± 15.7	52.8 ± 15.7	51.6 ± 15.9	0.704
Gender				
Female	99 (53%)	73 (73%)	26 (26%)	0.032*
Male	87 (47%)	75 (86%)	12 (14%)	
BSA, mean ± SD, m^2	1.65 ± 0.24	1.67 ± 0.24	1.59 ± 0.26	0.064
BMI, mean ± SD, (kg/m^2)	25.07 ± 8.64	23.53 ± 6.57	25.46 ± 9.07	0.218
Diagnosis				
Lower GIT	70 (37%)	58 (39%)	12 (32%)	-
Gynecological	24 (13%)	16 (11%)	8 (21%)	-
Breast	24 (13%)	18 (12%)	6 (16%)	-
Upper GIT	22 (12%)	16 (11%)	6 (16%)	-
Lung	18 (9.6%)	17 (11%)	1 (2.6%)	-
Urological	15 (8.0%)	14 (9.4%)	1 (2.6%)	-
Head and neck	8 (4.3%)	5 (3.4%)	3 (7.9%)	-
Skin	3 (1.6)	2 (1.3%)	1 (2.6%)	-
Bone	2 (1.1%)	2 (1.3%)	0	-
Concurrent chemotherapy				
5-FU-based	77 (41%)	65 (44%)	12 (32%)	0.168
Paclitaxel	42 (22%)	26 (18%)	16 (42%)	0.001
Gemcitabine	39 (21%)	30 (20%)	9 (24%)	0.645
Etoposide	17 (9%)	17 (12%)	0	0.026
Pemetrexed	6 (3%)	5 (3%)	1 (2%)	1.000
Capecitabine	3 (2%)	3 (2%)	0	1.000
Doxorubicin/Epirubicin	2 (2%)	2 (1%)	0	1.000
Baseline blood count				
Hb, mean ± SD, g/dL	11.1 ± 1.7	12.0 ± 1.8	10.9 ± 1.7	0.487
WBC, mean ± SD, $*10^3/L$	6.6 ± 2.9	6.6 ± 3.0	6.5 ± 2.5	0.912
ANC, mean ± SD, $*10^3/L$	4.3 ± 4.8	4.1 ± 4.3	4.9 ± 6.4	0.372
Eos, mean ± SD, $*10^3/L$	0.29 ± 0.70	0.32 ± 0.77	0.19 ± 0.20	0.291
Mono, mean ± SD, $*10^3/L$	0.64 ± 0.55	0.67 ± 0.6	0.53 ± 0.26	0.204
ALC, mean ± SD, $*10^3/L$	2.07 ± 1.6	1.99 ±1.01	2.3 ± 2.8	0.21
PLT, mean ± SD, $*10^3/L$	339 ± 144	336 ± 151	350 ± 118	0.594
Allergy to other medications	10 (5%)	7 (4.7%)	3 (7.9%)	0.427

HSR = hypersensitivity reaction; SD = standard deviation; BSA = body surface area; BMI = body mass index; 5-FU = 5-fluorouracil; GIT = gastrointestinal tract; Hb = hemoglobin; WBC = white blood cell; ANC = absolute neutrophil count; Eos = eosinophils; Mono = monocytes; ALC = absolute lymphocytes count; PLT = platelets.

Table 2. Predictors associated with hypersensitivity reaction (HSR).

Characteristic, n (%) unless specified otherwise	**All (N = 186)**	**Controls (N=148)**	**HSR (n = 38)**	***P* value**
Disease stage				
I	5 (2%)	3 (2%)	2 (5.3%)	0.557
II	18 (10%)	15 (9%)	3 (7.9%)	
III	37 (20)	31 (21%)	6 (16%)	
IV	126 (68)	99 (67%)	27 (71%)	
Previous lines of therapy				
Neoadjuvant	28 (15%)	21 (14%)	7 (18%)	0.441
Adjuvant	32 (17%)	28 (19%)	4 (11%)	
Palliative	126 (68%)	99 (67%)	27 (71%)	
Previous exposure to platinum	20 (11%)	16 (11%)	4 (11%)	1.000
Number of cycles, median (IQR)	9 (6-12)	9 (6-12)	8 (5-12)	0.431
Cumulative dose, median (IQR), mg	1890 (1200-3684)	1800 (1174-3615)	2075 (1352-3795)	0.446
Concomitant taxane therapy	42 (23%)	26 (17%)	16 (41%)	0.002
Concomitant radiotherapy	28 (15%)	15 (10%)	13 (35%)	<0.001

IQR, interquartile range.

Table 3. HSR grade according to NCI-CTCAEv4.0.

Grade of HSR	**No. of patients (% of cases)**
I	15 (39%)
II	15 (39%)
III	8 (21%)
IV	0