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ORIGINAL ARTICLE

Hypersensitivity reactions to platinum derivatives: findings of new predictive markers

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Summary

Purpose: *Platinum derivatives play a very important role in cancer therapy. Despite their outstanding results in the treatment of tumors with different locations, the occurrence of hypersensitivity reactions raises issues when it comes to therapy decision, because the changing of chemotherapy line could influence the tumor`s evolution. Over the years the scientific community has paid particular attention to the mechanism by which this occurs and to identification of predictive factors. The purpose of this case-control, retrospective study was to find new predictive markers for the occurrence of allergic reactions to platinum derivatives.*

Methods: *We identified 59 cases of allergic reactions to platinum derivatives in the Oncology Institute "Prof. Dr. Ion Chiricuta" from Cluj-Napoca city in 2013. Blood tests data were analyzed before the administration of the cycle on which the allergic reaction occurred, along with the mandatory analyses for the patients and we focused on the values of neutrophils, lymphocytes, monocytes, eosinophils and basophils.*

Results: *When these values were compared with the values of the control group (which was made at a ratio of 1:2 or 1:3, matched for age, tumor location and chemotherapy cycle) we found that each increase of lymphocytes or doses of platinum and each drop in monocytes number increased the risk for allergic reactions to occur.*

Conclusion: *These findings are of a great value for the physicians and represent a starting point for more detailed studies.*

Key words: *cancer, hypersensitivity, monocytes, platinum derivatives, predictive markers*

Introduction

Platinum derivatives had been introduced in therapy since the early 1980s and were mainly indicated in the therapy of malignant tumors of different origins. Up until today there are three compounds that are being used on a large scale: Cisplatin – the first generation, Carboplatin – the second generation, and Oxaliplatin – the third generation. On a smaller scale, other platinum derivatives that are being used are Nedaplatin – approved in Japan, Lobaplatin – approved in China, and Heptaplatin – approved in the Republic of Korea [1]. These drugs are essential for the treatment

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of cancers located in the stomach, lung and ovary. It is commonly known that platinum derivatives are liable for allergic reactions. Occurrence of allergic reactions to platinum compounds therapy raises issues when it comes to therapy decision. Changing the chemotherapy line can influence the disease evolution, as some tumors are less responsive to other drugs. Due to their frequently increased usage, the incidence of allergic reactions also increased [2]. Therefore, the incidence for Cisplatin is now between 5 and 20%, for Carboplatin between 9 and 27% and for Oxaliplatin between 10 and 19% [3,4].

Hypersensitivity reactions are body's modified reactions after contact with specific substances, microbial or chemical agents. Pathophysiologically, there are four types of allergic reactions, each with its own mechanism. The first type of hypersensitivity reaction is characterized by increased production of immunoglobulin E (IgE), taking place in two stages. After the body's first contact with the allergen, an increased quantity of IgE is synthesized and will be stored on basophils' and mastocytes' membrane, without any clinical symptoms occurrence. After repeated contacts with the allergen, basophils and mastocytes are activated, followed by their degranulation and the release of vasoactive mediators that cause clinical symptoms. Symptoms that accompany this type of allergic reaction are itching, chest pain, rash, anaphylactic reactions, and seasonal allergies [5,6]. Allergic reactions to platinum derivatives are usually of type I and they occur following multiple cycles of chemotherapy [7]. Hemolysis and thrombocytopenia, chronic urticaria, joint pain and proteinuria are considered to be type II and type III allergic reactions (mediated by IgG & IgM) to Oxaliplatin chemotherapy. The occurrence of inflammatory reactions hours or days after Oxaliplatin or Carboplatin therapy is considered to be a type IV allergic reaction and is mediated by T cells [8].

Over time, it has been attempted to optimize the tolerance of these compounds by implementing desensitization protocols [9,10], or by finding new markers with a predictive value in hypersensitivity reactions occurrence. Among these markers are skin testing, the number of chemotherapy cycles in which the allergic reaction has occurred, total dose of chemotherapy, previous allergies, lactate dehydrogenase values, gender, neutrophil and monocyte count [11-14]. Skin testing proved an efficient method, which unfortunately cannot be applied in every hospital.

The aim of this study was to assess the relationship between the values of the elements found in blood (basophils, leukocytes, monocytes, and eosinophils) and the risk of allergic reactions to platinum derivatives. We also made a relationship analysis between the chemotherapy dose, platinum derivative and the occurrence of allergic reactions.

Methods

This study was a case-control study, based on retrospective analysis of the database of The Oncology Institute "Prof. Dr. Ion Chiricuta" from Cluj-Napoca city, which is a regional oncologic hospital in North-West Romania, where patients from other regions are also treated.

We identified the occurrence of allergic reactions to platinum derivatives throughout the year 2013. Information was extracted from the database about patients with allergic reactions and control patients at a ratio of 1:2 or 1:3, matched for age, tumor location and chemotherapy cycle. Fifty-nine patients developed allergic reactions (group 1) and 142 did not (group 2, control group). The analyzed data included age, patient sex, allergic symptoms and their severity, re-challenge with the allergic agent, the type of chemotherapy regimen in which the allergic reaction had occurred, number of cycles after which the allergic reaction occurred, cumulative dose of platinum derivatives and previous exposure to them. The Ethics Committee of the Oncology Institute "Prof. Dr. Ion Chiricuta" has approved the protocol from which the data were analyzed.

All medical data obtained for the purpose of this study were strictly confidential. Any data that could allow patients to be identified were deleted from the database.

The blood analysis data was taken the same day, before the administration of the cycle in which the allergic reaction occurred, along with serum biochemistry (creatinine, bilirubin, alanine aminotransferase). The values of neutrophils, lymphocytes, monocytes, eosinophils and basophils were analyzed.

Statistics

Qualitative variables were calculated by the absolute numbers of lymphocytes, eosinophils, basophils and monocytes per μL and percentages. Quantitative data was presented by mean ± standard deviation if they followed a normal distribution, or median and interquartile range if they did not follow a normal distribution. Chi square test was used to test the relationship between qualitative variables. The comparison of two groups of quantitative data that followed a normal distribution was performed with Student's t-test for independent samples. Wilcoxon rank sum test and Kruskal-Wallis test were used to compare two groups and three groups of data that didn't follow a normal distribution. Nonparametric *post-hoc* tests were performed using Tukey contrasts. Normality of the data was as-

sessed with quantile-quantile plot and Shapiro-Wilk test. The area under the receiver operator characteristic (ROC) was computed along with 95% confidence interval (CI) obtained by bootstrap. A conditional logistic regression analysis was performed to predict allergic reactions based on platinum derivative type, age (years), gender, number of the cycle, first cycle (no/yes), total dose of chemotherapy (mg), the cumulative dose of chemotherapy (mg) (from the start of chemotherapy to the day when the allergic reaction occurred), leukocytes (10*3 /μL), neutrophils (10*3 /μL), lymphocytes (10*3 /μL), monocytes (10*3 /μL), eosinophils (10*3 /μL), and basophils (10*3 /μL). A full model was created with all these variables, then a stepwise backward/forward selection procedure was used to identify the variables in the final model, using Akaike information criterion. The results were presented as crude and adjusted odds ratios along with 95% confidence intervals. For all analyses a two-tailed p value less than 0.05 was considered statistically significant. The analyses were performed in R environment for statistical computing and graphics, version 3.2.0 [15].

Results

During 2013, 5800 cycles of Carboplatin, 2877 cycles of Cisplatin and 2080 cycles of Oxaliplatin were administered. There were 33 cases of allergic reactions to Carboplatin, 24 to Oxaliplatin and 2 to Cisplatin. Demographic data and other data regarding the 2 groups are summarized in Table 1.

The distribution of tumors' localization was as follows: bronchopulmonary 2 patients, cervix 6 patients, cholangiocarcinoma, 8 patients, melanoma 1 patient, ovary 23 patients, stomach 3 patients, colorectal carcinoma 14 patients, esophagus 1 patient, head and neck cancer (oropharynx) 1 patient. Regarding the chemotherapeutic regimen, 21 of patients received Carboplatin + Paclitaxel and 19 patients received Capecitabine + Oxaliplatin.

Hypersensitivity reactions were classified according to National Cancer Institute Common Criteria (NCI-CTCAE v4.0) as follows: 10.16% (6 patients) of the patients had grade 1 allergic reactions, 33.89% (20 patients) had grade 2, 54.23% (32 patients) had grade 3 and 1.6% (1 patient) had grade 4 allergic reactions.

The manifestations of allergic reactions were mainly located at cutaneous level (74.5%, 44 patients) and the respiratory system (64.41%, 38 patients); less affected were the circulatory system (37.29%, 22 patients) and the digestive system (23.9%, 20 patients). Manifested symptoms included dyspnea, bronchospasm, laryngospasm, erythema (face, limbs, and thorax), generalized pruritus, hypotension, abdominal pain, and nausea. The allergic reactions were managed by administering steroids, antihistamines, adrenaline, analgesics, antiemetics, and calcium and oxygen

Table 1. Characteristics of the study groups

Variables	*Allergic patients (N=59)*	*Control group (patients without allergic reaction) (N=142)*	*p value*
Age (years), mean (SD)	53.27 (12.26)	54.02 (10.63)	0.664
Female, N (%)	48 (28.74)	119 (71.26)	0.673
Male, N (%)	11 (32.35)	23 (67.65)	
Chemotherapy cycle, median (IQR)	3 (2 - 4)	2 (2 - 4)	0.241
[a] Chemotherapy dose when the allergic reaction occurred (mg), median (IQR)	1100 (520 - 2030)	975 (480 - 2037.5)	0.5
[b] Chemotherapy dose of previous exposures (mg), median (IQR)	0 (0 - 3300)	0 (0 - 0)	< 0.001
[a+b]Total dose of chemotherapy (mg), median (IQR)	2110 (750 - 5200)	1140 (500 - 3407.5)	0.016
Leukocytes (10*3 /μL), median (IQR)	6.11 (4.66 - 7.45)	5.56 (4.68 - 7.09)	0.471
Neutrophils (10*3 /μL), median (IQR)	3.4 (2.42 - 4.58)	3.18 (2.33 - 4.07)	0.382
Lymphocytes (10*3 /μL), median (IQR)	1.84 (1.33 - 2.15)	1.77 (1.19 - 2.14)	0.505
Monocytes (%), median (IQR)	10.8 (8.25 - 12.7)	10.7 (8.8 - 14.1)	0.281
Monocytes (10*3 /μL), median (IQR)	0.62 (0.44 - 0.86)	0.62 (0.51 - 0.79)	0.717
Eosinophils (%), median (IQR)	0.9 (0.45 - 2)	1.4 (0.7 - 2.5)	0.04
Eosinophils (10*3 /μL), median (IQR)	0.06 (0.02 - 0.13)	0.07 (0.04 - 0.15)	0.095
Basophils (%), median (IQR)	0.3 (0.2 - 0.5)	0.4 (0.2 - 0.6)	0.178
Basophils (10*3 /μL) , median (IQR)	0.02 (0.01 - 0.03)	0.02 (0.01 - 0.04)	0.263

[a]: mg values for chemotherapy dose when the allergic reaction occurred, [b] : mg values for chemotherapy dose of previous exposures, [a+b] : mg values for total dose of chemotherapy, SD : standard deviation, IQR : interquartile range

Table 2. Predictive factors for the occurrence of allergic reactions found using a conditional logistic regression

Variables	*Crude OR (95% CI)*	*p value*	*Adjusted OR (95% CI)*	*p value*
Platinum derivative (Cisplatin vs Carboplatin)	1.63 (0.29 – 9.29)	0.580	2.47 (0.39 – 15.71)	0.338
Platinum derivative (Oxaliplatin vs Carboplatin)	1.19 (0.67 – 2.11)	0.556	2.83 (1.28 – 6.26)	0.010
First cycle (no vs yes)	2.45 (0.79 – 7.64)	0.123	3.44 (0.996 – 11.85)	0.051
Chemotherapy total doses (mg)	1 (1.00 – 1.00)	0.032	1.000 (1.00 – 1.0002)	0.001
Lymphocytes (10*3/μL)	1.18 (0.82 – 1.69)	0.369	1.61 (1.04 – 2.47)	0.032
Monocytes (10*3/μL)	0.79 (0.32 – 1.95)	0.615	0.27 (0.77 – 0.94)	0.040
Neutrophils (10*3 /μL)	1.03 (0.91 – 1.19)	0.615	1.18 (0.98 – 1.40)	0.073

OR : odds ratio, CI : confidence interval

therapy. Adrenaline and oxygen therapy were administered only in severe cases.

After the onset of the allergic episode, 49.15% (29/59) of the patients were re-challenged to chemotherapy and 52.63% (10/29) of them still showed allergic reaction.

Regarding chemotherapy doses at previous exposures, the total dose of chemotherapy administered to the patients and the occurrence of hypersensitivity reactions, we found statistically significant difference between the two groups. We also found that the allergic reactions occurred after a median of 360 days (range 260-534) of free platinum interval for Carboplatin and 255.5 days (range 178.75-460.25) for Oxaliplatin. These values were calculated for the allergic patients who were previous exposed to Carboplatin or other platinum derivatives (20 of 33 patients) and Oxaliplatin or other platinum derivatives (8 of 24 patients).

The cycle number was different between platinum derivatives (overall p=0.005), statistical differences being found between Carboplatin [median interquartile range (IQR)=3 (2–5)] and Oxaliplatin [median IQR=2 (2–3)] that had lower values (p<0.001), and between Cisplatin [median IQR=3 (3–4)] and Oxaliplatin (p<0.01), but not between Carboplatin and Cisplatin (p=0.167).

The area under the receiver operator characteristic (AUROC) for allergic reactions based on exposure dosage was 0.53 (95% CI 0.45-0.62) for all the subjects; cut-offs were not computed. For patients who received Carboplatin AUROC was 0.55 (95% CI 0.43-0.66), for those who received Oxaliplatin was 0.61 (95% CI 0.47-0.75), and for Cisplatin there were too few subjects to compute.

Regarding the blood count, the percents of eosinophils were statistically significantly lower in patients that showed allergic reactions (p=0.04), while for absolute values of eosinophils the difference was not statistically significant between the two groups (p=0.095).

Each increase of lymphocytes or doses of platinum derivatives increased the risk of allergic reactions to occur, and each drop in monocytes number increased the risk for allergic reactions to occur. Oxaliplatin showed the highest risk of allergic reactions occurrence (Table 2).

Discussion

It is known that high doses and previous exposures to platinum derivatives increase the risk of allergic reactions occurrence [8,10] and our study confirmed these findings (Table 1). International guidelines (NCCN) recommend the use of desensibilisation, in order to preserve an active line of treatment. For now no definitive predictive factors have been recognized and accepted in guideline recommendations.

A study of Piovano et al. found as risk factors for hypersensitivity reactions in patients with gynecologic malignancies treated with Carboplatin the following: 1) menopausal status and body mass index >25 showed a lower risk; 2) a history of systemic hypersensitivity showed a higher risk; and 3) age was not associated with a higher risk. The same study confirmed that the incidence of hypersensitivity reactions was higher in ovarian cancer [13]. Regarding the Oxaliplatin therapy, Kim et al. found as risk factors for the occurrence of hypersensitivity reactions the following: 1) younger age; 2) female sex; and 3) use of Oxaliplatin as salvage therapy [16,17]. In our study no statistical differences were noticed regarding gender or age of the patients.

The present study found that the average number of administrations after which allergic

reactions occurred was three cycles for Carboplatin and Cisplatin and two cycles for Oxaliplatin, although literature states that allergic reactions develop after at least four courses of chemotherapy. We also found that previous exposure to platinum derivatives, the dose administered at the chemotherapy regimen when the allergic reaction occurred, the total dose of chemotherapy (previous+current exposure) were higher in patients with allergic reactions (Table 1) and each increase in chemotherapy dose increased the risk of allergic reaction (Table 2). Couraud et al. reported that besides the number of administered courses as risk factors, previous exposure to platinum salts, third line of treatment and a long platinum free interval were risk factors [18], some of them being described by other authors too [19]. An interesting fact is that in some cases Carboplatin didn't show cross-hypersensitivity with Cisplatin. If a patient is allergic to Carboplatin, he might tolerate Cisplatin and *vice versa* [19,20].

Hypersensitivity reactions to Oxaliplatin were considered less frequent, but the increase of its usage also increased the absolute number of hypersensitivity reactions [8]. Our study not only confirmed this, but also found that the risk for allergic reactions to Oxaliplatin was 2.8 -fold higher than Carboplatin (Table 2). Other studies had found that the incidence of allergic reactions to platinum derivatives is 5-10% for Cisplatin, 9-27% for Carboplatin and 10-19% for Oxaliplatin [17]. As mentioned before, intensive use of Oxaliplatin showed an increased incidence of hypersensitivity for Oxaliplatin which raised from 2% in initial trials to actual high occurrence of 10-25% [21].

We found that the most frequent incriminated localization and chemotherapy regimen were colon and ovary, Oxaliplatin + Capecitabine and Carboplatin + Paclitaxel, respectively.

Our study showed no difference between the two groups of patients in terms of basophils' number, though literature states differences in terms of quality regarding the basophils. A study of Iwamoto et al. showed that monitoring pharmacodynamic changes (overexpression of FcεR1) on basophils after repeated exposures to Carboplatin is an important marker for severe allergic reactions to Carboplatin [22].

Eosinophils represent up to 1-6% of the total white blood cells. Their role is to destroy parasites and microorganisms but are also responsible for amplifying the inflammatory response. An ever increasing number of studies are focusing on their role in the pathogenesis of allergic asthma, the meaning of this condition is highlighted and the eosinophils can be considered as a future therapeutic target as some studies show [23-26]. In the present study, after analyzing the eosinophils' values, we noticed that in patients who developed an allergic reaction, the percentage of eosinophils was lower compared to the control group but this could be explained by the variation of the values of other leukocytes. Another explanation could be related with the severity of hypersensitivity. A study of Kyoko et al. showed that the percentage of eosinophils found in patients with grade 3 or 4 allergic reactions to Oxaliplatin was lower compared to the control group (statistically insignificant). In our patients, 54.23% developed grade 3 hypersensitivity reactions, thus the decrease in eosinophils' percentage could be explained by the grade of the allergic reaction. Comparison of the number and percentage of eosinophils in the two groups shows an elevation in the number of eosinophils in the control group, but without statistical significance. On the contrary, Okayama et al., in their publication, showed that eosinophils were significantly increased in patients with hypersensitivity reaction, compared with the control group. Eosinophil count has been proved as independent predictive factor for hypersensitivity reaction for Oxaliplatin [27]. Mori et al. found that Oxaliplatin free interval could represent a risk factor for hypersensitivity reaction [28], while Shao et al. found that rechallenge with Oxaliplatin increased the risk of hypersensitivity reaction up to 71.4% [29].

When it comes to lymphocytes and monocytes, no statistically significant differences between patients that developed allergic reactions and the control group were noticed. The novelty that our study brings is that these elements (lymphocytes, monocytes, eosinophils and Platinum cumulative dose) might play a predictive role in hypersensitivity reactions to Platinum derivatives (Table 2). Although it has been reported a lower monocyte count in patients which developed allergic reactions to Platinum derivatives [14], to our knowledge this is a first-time report of a relationship between their values and the risk of an allergic reaction. Seki et al. suggested that high numbers of eosinophils are correlated with low grade hypersensitivity reaction meanwhile high grade hypersensitivity reaction is linked to high numbers of monocytes [14,30].

Regarding the limitations of this study we can quote the small number of clinical reports of

the allergic reactions, incomplete data about the associated pathologies of the patients, the small number of patients which developed allergic reactions and the fact that we could not establish a predictive dose for the occurrence of hypersensitivity reactions.

Conclusion

Our study achieved its purpose of finding new predictive markers for the appearance of allergic reactions to platinum derivatives. It has also found that each increase of lymphocytes or doses of platinum derivatives increases the risk of allergic reactions to occur, and each drop in monocytes increases the risk for allergic reactions to occur. These findings can constitute the basis of future research regarding the establishment of non-invasive, low-cost markers for the occurrence of allergic reactions to platinum derivatives.

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