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Original Paper

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Analysis of the toxicity induced by carboplatin and paclitaxel regimen in ovarian cancer patients

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Abstract

Objective: To analyze the toxicities induced by the carboplatin and paclitaxel regimen in ovarian cancer patients, seeking to identify possible risk factors related to its occurrence and clinical interventions. **Method:** A retrospective cohort study was conducted involving ovarian cancer patients, enrolled between 2015 and 2017 at a reference oncology hospital in Brazil. The following data were collected from medical records and prescriptions: demographic, clinical and pharmacotherapeutic; the information on toxicities induced by treatment; and clinical interventions (chemotherapy dose reduction, chemotherapy suspension, and change of treatment regimen). The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) code. The toxicities were classified as to their severity according to the Common Terminology Criteria for Adverse Events. A descriptive analysis of the variables was performed, the relative risk was calculated, and Fisher's exact test was used to check for possible associated risk factors. A p-value<0.05 was adopted as statistical significance. **Results:** The study included 105 patients. Of these, 47% had some comorbidity, 71% were polymedicated, 2% were exposed to drug interactions with the studied regimen, and 73% had toxicities, 35% of which were grade > 2. Alopecia and asthenia were the most severe toxicities, and 55% had at least one of the clinical interventions studied, which resulted in a worse prognosis. Women under the age of 60 had a higher risk of developing toxicities (51.0%; p=0.038), while those with stage III presented a lower risk (24.0%; p=0.052). Of the total, 40.9% (n=43) of the women had some clinical intervention recorded. Dose reduction was the most common clinical intervention (48.8%, n=21), with severity of the toxicities the main cause (57.1%, n=12). No association was observed between the variables investigated and the occurrence of toxicities grade > 2. **Conclusions:** The study was able to identify the main toxicities that occur with ovarian cancer patients treated at the institution and has the potential to assist health professionals in carrying out preventive and clinical measures related to the severity of the toxicities that the treatment with the investigated regimen can cause.

Key words: ovarian cancer; drug toxicity; chemotherapy; cohort study.

Análise de toxicidades relacionadas ao protocolo carboplatina e paclitaxel em pacientes com câncer de ovário

Resumo

Objetivo: analisar as toxicidades induzidas pelo protocolo carboplatina e paclitaxel em pacientes com câncer de ovário, buscando identificar os possíveis fatores de risco relacionados à sua ocorrência e as intervenções clínicas. **Método:** realizou-se um estudo de coorte retrospectivo envolvendo pacientes com câncer de ovário, matriculadas entre 2015 e 2017 em um hospital oncológico de referência no Brasil. Foram coletados dos prontuários e receitas médicas: dados demográficos, clínicos e farmacoterapêuticos; informações sobre toxicidade induzida pelo tratamento; e intervenções clínicas (redução da dose de quimioterapia, suspensão da quimioterapia, e alteração do regime de tratamento). Os medicamentos foram classificados segundo o código Químico-Terapêutico-Anatômico (ATC). As toxicidades foram classificadas quanto à gravidade de acordo com os Critérios Terminológicos Comuns para Eventos Adversos. Foi realizada análise descritiva das variáveis e calculado o risco relativo. Utilizou-se o teste exato de Fischer para verificar os possíveis fatores de risco associados. Foi assumido um valor de p < 0,05 como significância estatística. **Resultados:** foram incluídos 105 pacientes. Destes, 47% tinham alguma comorbidade, 71% estavam polimedicados, 2% estavam expostos a interações medicamentosas com o regime estudado, 73% apresentaram toxicidade, sendo 35% destas de grau > 2. Alopecia e astenia foram as toxicidades mais graves, e 55% tiveram pelo menos uma intervenção clínica, o que resultou num pior prognóstico. As mulheres com menos de 60 anos tiveram um risco mais elevado de desenvolver toxicidade (51,0%; p=0,038), enquanto que as mulheres com estadiamento III tiveram um risco mais baixo (24,0%; p=0,052). Do total, 40,9% (n=43) das mulheres tiveram alguma intervenção clínica registada. A redução da dose foi a intervenção mais comum (48,8%, n=21), sendo a causa principal a gravidade das toxicidades (57,1%, n=12). Não foi observada qualquer associação entre as variáveis investigadas e a ocorrência de toxicidade de grau > 2. **Conclusões:** o estudo foi capaz de identificar as principais toxicidades que acometeram mulheres com câncer de ovário tratadas na instituição, e tem potencial para auxiliar os profissionais da saúde na realização de medidas preventivas e intervenções clínicas relacionadas à gravidade das toxicidades que o tratamento com o protocolo investigado pode causar.

Palavras chave: câncer de ovário; toxicidade de medicamentos; quimioterapia; estudo de coorte.

Introduction

Ovarian cancer is the most difficult gynecological tumor to diagnose and the one with the lowest probability of cure[1]. Almost 75% of tumors in this organ are in advanced stage at the time of diagnosis[2]. The absence of clear symptoms of the disease and the lack of specific screening are among the reasons for this outcome[3].

Worldwide, 313,359 new cases and 207,252 deaths due to ovarian cancer were estimated in 2020[4]. In Brazil, for the period 2020-2022, 6,650 new cases of ovarian cancer were estimated per year, and it isthe seventh most common type of cancer among women[5]; and an increase in the mortality trend due to this tumor has been observed over the years[6].

Most ovarian tumors are epithelial carcinomas; however, there are two other histological types: malignant germ cell tumor and stromal tumors[7]. In epithelial tumors, the cells have characteristics that are used to classify them into different types. The serous type is the most common, in addition to the mucinous, endometrioid and clear cell types[2]. The tumor is called undifferentiated when the cells do not resemble any of the four subtypes, and tend to grow and spread more rapidly[8].

The treatment used will depend on the histological type of the tumor, the stage of the disease and the patient's clinical and demographic factors, with the possibility of surgery and/or chemotherapy (CTX)[9]. For primary ovarian cancer, standard CTX involving the combination of taxane and platinum-based drugs such as paclitaxel and carboplatin, has been indicated as the first line of treatment for over two decades[10-11].

The use of these drugs is not without risks, since they can cause hematological toxicities, neuropathies, fatigue, nausea and other events[12-13]. The occurrence of severe toxicities may require dose reduction or treatment delay or interruption, demanding clinical interventions and/or impairing disease prognosis[14]. To prevent the occurrence or minimize the severity of toxicities, the use of supportive drugs associated with the combination of CTX is a common and recommended practice[15], especially to improve the quality of life of women undergoing treatment[1]. In addition, ovarian cancer patients may present comorbidities[16] and require the use of other drugs that may potentiate toxicities or favor drug interactions (DIs), compromising the safety and efficacy of the therapy adopted, due to polypharmacy[17].

Knowledge about the possible risk factors for toxicity in cancer patients helps health professionals to improve their practices and ensure patient safety[18]. Despite the existence of several clinical trials evidence, studies with real-life data on this topic and involving ovarian cancer patients are few[19].

This study aimed to analyze the occurrence of toxicities in ovarian cancer patients treated with the carboplatin-paclitaxel (CP) regimen in a high-complexity oncology center, seeking to identify possible risk factors related to its occurrence and clinical interventions.

Methods

A retrospective cohort study was conducted in a specialized public hospital located in Rio de Janeiro, Brazil, a reference for the treatment of gynecological tumors.

All women diagnosed with epithelial ovarian cancer of the adenocarcinoma type confirmed by histopathological exam, between 2015 and 2017, older than 18 years of age and treated with the CP regimen at the institution were considered eligible. Women excluded from the analysis were those who had already undergone cancer treatment, as well as those diagnosed with undifferentiated ovarian cancer or with remote metastasis (Stage IV).

The CP regimen used at the institution involves intravenous infusion on day 1 (D1) of pre-CTX drugs (dexamethasone 20 mg, ondansetron 8 mg, ranitidine 50 mg and diphenhydramine 50 mg), followed by intravenous infusion of chemotherapy drugs (paclitaxel 175 mg/m² and carboplatin AUC (area under the curve) of 4 to 6). A new cycle is performed after 21 days until a total of 6 cycles are completed[20]. After each CTX cycle, in order to prevent nausea and vomiting, the following therapeutic regimen is planned: dexamethasone 4 mg every 12 hours for 3 or 4 days + ondansetron 8 mg every 12 hours for 3 or 4 days + metoclopramide 10 mg every 6 hours for 5 days[20].

Data were collected from May to November 2018. A form that was exclusively prepared for the study was used for data collection.

Sociodemographic and clinical data were collected from the medical charts and electronic medical records, from the period of admission until the last cycle of the CP regimen. The sociodemographic data recorded were the following: age (in complete years), marital status (single, married, divorced, widowed), skin color (white, brown, black), schooling (elementary school, high school, college education, illiterate), professional activity (yes or no), smoking (yes or no) and alcohol consumption (yes or no). Age in completed years was recorded at the time of admission. Patients considered to be smokers were all those with a history of smoking, even if they self-reported as former smokers. Patients identified as drinkers were those in whom any information about alcohol consumption was recorded, even if low frequency of consumption was indicated in the medical chart.

The clinical data collected were as follows: histological subtype of the tumor (serous, mucinous, endometrioid, rare cells, mixed and papillary), disease staging (I, II and III), type of CTX (neoadjuvant, adjuvant and palliative), number of cycles performed, and presence and type of comorbidity.

In order to search for information regarding pharmacotherapeutic data, the systems containing the institution's electronic medical records and prescription were used (INTRANET and ABSOLUTE®). The following variables were collected: drugs used concomitantly with CTX; presence of polypharmacy (use of 5 or more drugs – including regular and emergency drugs); use of drugs with potential for interaction with the CP regimen. Upon accessing INTRANET, the prescription prior to each CTX cycle was searched. Each prescription had a unique identification number and was imported into ABSOLUTE®. In this system, the prescriptions were analyzed and it was possible to obtain the names of the continuous and emergency drugs that were prescribed and dispensed by the hospital's outpatient pharmacy to be used togheter with the CP regimen. Consequently, it was possible to identify the drugs that patients were receiving for their treatments.

The drugs were classified according to the *Anatomical Therapeutic Chemical* (ATC) code[21]. The first level– major anatomical group – was used to classify the drugs according to the number of dispensings performed by the pharmacy. The fifth level – chemical substance – was used when considering the number of patients that had the drugs prescribed.

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To characterize the presence of polypharmacy, the total of numbers of drugs prescribed and dispensed for each patient was considered, with the exception of those used in pre-CTX and in the CP regimen.

To identify wheter the patient used any drug with the potential to interact with the regimen, an analysis was performed on the *Drugs.com Statistics*® database[22]. The priority was to identify only those drugs with a potential for moderate or severe interactions, according to the baseline classification. Only those drugs that were standardized and dispensed by the outpatient pharmacy of the study unit were considered in the analysis (Figure 1). Patients who received a drug with potential interactions were identified as exposed to DIs.

Figure 1. Classification of the potential for drug interactions between the carboplatin-paclitaxel (CP) regimen and other standardized drugs dispensed by the outpatient pharmacy of a high-complexity oncology center in the state of Rio de Janeiro - Brazil.

Drugs of the Carboplatin-Paclitaxel (CP) regimen	Severe drug interaction	Moderate drug interaction
Carboplatin	Warfarin Phenytoin	Not described
Paclitaxel	Clopidogrel	Phenytoin
Dexamethasone	Nifedipine	Phenytoin Acetylsalicylic acid (ASA) Warfarin Phenytoin Rifampicin
Ondansetron	Not described	Not described
Ranitidine	Ketoconazole	Warfarin Risperidone
Difenidramine	Not described	Not described

Sources: Drugs.com Statistics®; December, 2020.

The collection of data related to toxicities in patients during treatment and clinical interventions (CTX dose reduction, CTX suspension and regimen change) occurred through the analysis of the medical charts and electronic medical records. An attempt was made to record these variables from the first CP cycle until two weeks after the last cycle performed. The identified toxicities were classified in terms of their severity, according to the health professionals' record in the classification (grade 1, 2, 3, 4 or 5), using the Common Terminology Criteria for Adverse Events - version 5.0 as a basis[23]. The institution has a pharmacovigilance service. In cases when it was necessary to validate the information, the service was duly consulted.

The data were organized in Microsoft Excel® spreadsheets and the statistical analyses were performed in *Stata*®, version 12.0. A descriptive analysis of the demographic, clinical and pharmacotherapeutic variables was performed. The relative risk was calculated. Fisher's exact test was used to verify the possible association between the variables investigated and the occurrence of toxicities, as well as between the toxicities recorded in medical records with ≥ grade 2 severity and the clinical interventions analyzed. The statistical significance level adopted was p-value < 0.05.

The project was approved by the institution's Ethics and Research Committee (*Comitê de Ética e Pesquisa*, CEP) (CAAE: 87648118.9.0000.5274). There was a waiver to obtain a Free and Informed Consent Form (FICF) because this is a retrospective and non-interventional study with anonymous and aggregated data analysis without adding risks or loss to participants.

Results

A total of 139 patients were eligible for the study, of which 39 were excluded due to Stage IV diagnoses and four due to undifferentiated tumor diagnosis. Finally, 105 patients were included in the analyses.

The median age was 57 years ~~old~~ (min=26; max=79). The characterization of the demographic and clinical profile is presented in Table 1. Most patients were unmarried, self-reported as white-skinned, with elementary schooling, no work activity at admission, and did not smoke or drink alcohol. Regarding their clinical profile, most had serous histological subtype and Stage III. Adjuvant chemotherapy was the most indicated and the median number of CTX cycles performed was 6 (min=1; max=8). Almost half of the patients had some type of comorbidity reported in their medical records. Of these, 53.1% had hypertension, 32.7% hypertension+diabetes, 4.1% diabetes, 4.1% dyslipidemia, 2.0% heart disease, 2.0% nephropathy and 2.0% obesity.

Table 1. Characterization of the sociodemographic and clinical profile of the patients with adenocarcinoma-type epithelial ovarian cancer, diagnosed between 2015 and 2017 and treated with the carboplatin and paclitaxel (CP) regimen at a high-complexity oncology center in the state of Rio de Janeiro - Brazil

Variable	n	%
Marital status		
Married	36	34.3
Single	36	34.3
Widow	20	19.0
Divorced	13	12.4
Skin color		
White	57	54.3
Brown	38	36.2
Black	10	9.5
Schooling		
Elementary school	56	53.3
High School	37	35.2
Higher Education	11	10.5
Illiterate	1	1.0
Work activity		
No	62	59.0
Yes	43	41.0
Smoking		
No	76	72.4
Yes	29	27.6
Drinking habit		
No	93	88.6
Yes	12	11.4
Histological type of the tumor		
Serous	65	61.9
Mucinous	14	13.3
Clear cells	13	12.4
Endometrioid	9	8.6
Mixed	2	1.9
Papilliferous	2	1.9
Tumor stage		
III	74	70.5
I	17	16.2
II	14	13.3
Type of chemotherapy		
Adjuvant	64	60.9
Neoadjuvant	32	30.5
Palliative	9	8.6
Comorbidity		
No	56	53.3
Yes	49	46.7

All the patients used at least one drug concomitantly with CTX. Most of the drugs dispensed by the outpatient pharmacy were for treating health problems related to the digestive tract and metabolism. The most frequently used drugs were dexamethasone, ondansetron and dipyrone. More than 70% of the patients were polymedicated. Two patients were exposed to DIs with the regimen under study. The pharmacotherapeutic profile is shown in Table 2.

Table 2. Characterization of the sociodemographic and clinical profile of the patients with adenocarcinoma-type epithelial ovarian cancer, diagnosed between 2015 and 2017, and treated with the carboplatin and paclitaxel (CP) regimen at a high-complexity oncology center in the state of Rio de Janeiro - Brazil

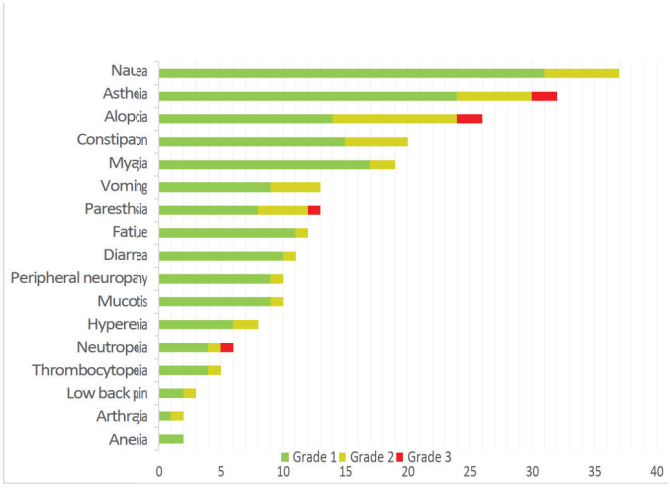
Variable	n	%
Anatomical Therapeutic Chemical (ATC) Group (Total = 861)		
Alimentary tract and metabolism (A)	517	60.0
Nervous system (N)	213	24.7
Respiratory system (R)	46	5.3
Anti-infectives for systemic use (J)	28	3.3
Blood and blood forming organs (B)	22	2.6
Cardiovascular system (C)	22	2.6
Musculoskeletal system (M)	5	0.6
Antineoplastic and immunomodulating agents (L)	4	0.5
Antiparasitic products, insecticides and repellents (P)	4	0.5
Drugs most used by the patients (Total = 105)		
Dexamethasone (A01AC02)	98	93.3
Ondansetron (A04AA01)	95	90.5
Metamizole sodium (N02BB02)	86	81.9
Omeprazole (A02BC01)	64	61.0
Bromopride (A03FA04)	63	60.0
Metoclopramide (A03FA01)	53	50.5
Tramadol (N02AX02)	33	31.4
Codeine (N02AA59)	22	21.0
Loperamide (A07DA03)	21	20.0
Paracetamol (N02BE01)	21	20.0
Polypharmacy		
No	30	28.6
Yes	75	71.4
Potential drug interaction with the protocol		
No	103	98.1
Yes	2	1.9

In relation to the profile of the two patients that were exposed to DIs with the CP regimen, both were hypertensive and took acetylsalicylic acid (ASA) at a dose of 100 mg once daily. One of them finished all six treatment cycles without any record of toxicity or negative outcome. The other patient presented thrombocytopenia, classified as Grade 2, with the need to discontinue ~~the~~ treatment and change the CTX regimen.

With regard to toxicities, 73.3% of ~~the~~ patients had some report in their medical records in at least one of the cycles. The health professionals classified 76.9% of the 229 toxicities reported as Grade 1, 20.5% as Grade 2 and 2.6% as Grade 3. No Grade 4 or 5 toxicities were identified. 17 types of toxicities were reported, with nausea being the most frequent. Figure 2 presents the types of toxicities reported in the medical records, according to ~~the~~ severity classification.

Among ~~the~~ women who had some type of toxicity, 70.1% were between 18 and 59 years of age, 66.2% were unmarried, 58.4% were white-skinned, 51.9% had attended only elementary school, 61.0% were not working, 70.1% were not smokers, 89.6% did not consume alcohol, 58.6% had the serous histological subtype, 64.9% had stage III at diagnosis, 66.2% had adjuvant CTX, 85.7% had undergone between six and eight cycles of the CP regimen, 50.6% had no comorbidities, and 72.7% were polymedicated.

Figure 2. : Types of toxicities according to severity classification, reported in the medical records of the patients with adenocarcinoma-type epithelial ovarian cancer, diagnosed between 2015 and 2017 and treated with the carboplatin and paclitaxel regimen (CP) at a high-complexity oncology center in the state of Rio de Janeiro- Brazil

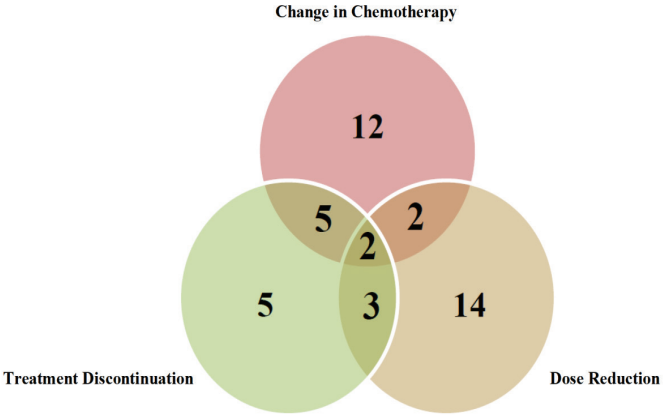


When the possibilities ~~of~~ association of ~~the~~ sociodemographic, clinical and pharmacotherapeutic variables with the occurrence of toxicities were analyzed, a positive association was identified for age and stage. Women under 60 years of age had a 51.0% higher risk of developing toxicities when compared to ~~the~~ patients aged 60 years or older (RR=1.51; CI=1.05-2.17; p=0.038). Women diagnosed with Stage III had a 24.0% lower risk of developing toxicities when compared to the patients in early stages – I or II (RR=0.76; CI=0.58-0.99; p=0.052).

Of the total, 40.9% (n=43) of the women had some record clinical intervention. Of these, 72.1% were between 18 and 59 years old, 62.8% were unmarried, 62.8% were white-skinned, 41.9% had attended only elementary school, 60.5% were not working, 65.1% were not smokers, 88.4% were not drinkers, 67.4% had the serous histological subtype, 69.8% had been in Stage III at the time of diagnosis, 58.1% had performed adjuvant CTX, 67.4% had undergone six or more cycles of the CP regimen, 60.5% had no record of comorbidity, 67.4% were polymedicated, and 79.1% had experienced at least one toxicity during treatment. Among the variables analyzed, ~~the~~ women who underwent between six and eight treatment cycles were 27.0% less at risk for any of the interventions analyzed when compared to those who underwent fewer than six cycles (RR=0.73; CI=0.61-0.89; p=0.002).

Figure 3 shows the distribution of recorded clinical interventions. It can be observed that, in some cases, the team initially tried to reduce the CTX dose before discontinuing the treatment and/or changing the regimen. In other situations, regimen change was the team's first choice before deciding to discontinue CTX.

Figure 3. Clinical interventions recorded in the medical records of patients with adenocarcinoma-type epithelial ovarian cancer, diagnosed between 2015 and 2017 and treated with the carboplatin and paclitaxel (CP) regimen at a high-complexity oncology center in the state of Rio de Janeiro- Brazil



Among the patients that had their CTX dose reduced (n=21), 85.7% reduced their paclitaxel dose (four had their dose reduced by 10%, ten by 15% and four by 20%). The carboplatin dose reduction was necessary due to the AUC adjustment from 5 to 4, in three cases. The reasons for dose reductions were as follows: severity of the toxicities (57.1%, n=12), disease progression (28.6%, n=6), decline in Performance Status (9.5%, n=2) and presence of comorbidities (4.8%, n=1). Among the patients who had their CTX regimen changed (n=21), one had a record of severe toxicity as the reason and three displayed disease progression. In turn, among those that had their treatment interrupted (n=15), three had records of severe toxicity and two, of disease progression.

In total, 41.9% of the women had toxicity grades $\geq$ 2. No positive association of demographic, clinical and pharmacotherapeutic parameters with the occurrence of more severe toxicities could be identified. The same was noted for clinical interventions. The relative risk of toxicity grade > 2 for CTX dose reduction was 1.48 (CI=0.83-2.65; p=0.208), for treatment discontinuation was 1.40 (CI=0.72-2.71; p=0.385) and for regimen change it was 1.10 (CI=0.59-2.08; p=0.801).

Discussion

The study showed that most ovarian cancer patients treated with the CP regimen were susceptible to toxicities. Severe toxicities related to asthenia, alopecia, paresthesia and neuropathy were identified, requiring a higher level of attention and care from the healthcare team. Age less than 60 years and early cancer staging (I and II) were identified as potential predictors of toxicities. Dose reduction and changing the chemotherapy regimen were the most commonly used strategies by the healthcare team to minimize the effects of toxicities in the patients studied. Although it was not possible to make an association between clinical interventions and the severity of the identified toxicities, all the information obtained is of fundamental importance to structure the care provided to patients undergoing treatment.

In relation to the demographic, clinical and pharmacotherapeutic profiles, it should be noted that not much information is available in the literature on how these variables may affect the treatment of women with ovarian cancer. This study obtained results that may help in this discussion. One of the data identified was the occurrence of a higher incidence of toxicities in younger patients. The literature indicates that there is no difference in treatment tolerance with the CP regimen attributed to the patients' age[24]; however, it is common to find adoption of non-standardized regimens, with dose reductions for older adults[25]. A similar situation is observed in early staged patients, who were more susceptible to the occurrence of toxicities. Patients with more advanced disease usually have their treatments adjusted, with administration of intraperitoneal chemotherapy, to minimize the occurrence of toxicities[26]. From this perspective, it is possible to assume that younger patients and those in early staging may be more exposed to treatment patterns capable of promoting toxicities, since these women generally have better clinical conditions at diagnosis.

Regarding the pharmacotherapeutic profile, one of the data found was the low frequency of identified DIs, which may be related to the profile of the multiprofessional team of the institution and the adoption of preventive strategies. In cases where potential DIs were observed, it should be noted that ASA interacts moderately with dexamethasone, as shown in Figure 01. According to *Drugs.com*®, this interaction decreases serum ASA concentrations, increasing the risk of thrombosis in patients[22]. One of the patients exposed to DIs required CTX suspension and regimen change due to the occurrence of grade 2 thrombocytopenia. Although this fact is not related to the interaction between ASA and dexamethasone drugs, healthcare teams should be vigilant. The presence of thrombocytopenia may increase the risk of bleeding complications and may require a reduction in anticoagulant doses, implying a greater susceptibility to the development of thrombosis in patients undergoing anticancer therapies[27].

When analyzing the supporttive drugs used by the patients in the study, it was observed that they used mainly drugs to control nausea and vomiting, for gastric protection and for pain control, pointing to a broad adherence of the healthcare team to protocols for prevention and treatment of toxicities related to the CP regimen[28]. However, despite of the fact that 93% and 90% of patients were using dexamethasone and ondansetron, respectively, to control nausea and vomiting, only 50% used metoclopramide, which is also found in the post-CTX regimen used at the institution[20]. This partial support for the protocol may account for the fact that nausea is one of the main toxicities identified in the study, pointing to the limited effectiveness of the protocol used to prevent emesis. The need to intensify the proper use of the post-CTX regimen by expanding adherence to the metoclopramide prescription or, alternatively, proposing a change in the protocol to make nausea and vomiting control more effectiveby including more powerful drugs such as aprepitant[29] is emphasized.

Despite the lack of statistical significance, it drew attentionto the fact that almost 70% of patients with toxicity grade > 2 were polymedicated. It is known that ovarian cancer patients have multiple comorbidities and therefore the use of multiple drugs often becomes unavoidable[17]. However, the clinical relevance of this finding reinforces the importance of professionals being attentive to the adoption of measures that promote rational use of drugs, mainly evaluating the need for use and the possibility of deprescribing some drugs[30], in order to prevent patients from being exposed to risks of DI and the most severe toxicities.

Gockley *et al.*[28] showed that chemotherapy treatment of ovarian cancer can lead to several toxicities. According to the study, more

than half of ovarian cancer patients undergoing chemotherapy are affected by peripheral neuropathy, in addition to other toxicities considered common, such as: sexual dysfunction; gastrointestinal disorders (nausea, vomiting, constipation and diarrhea); cognitive dysfunction; mood swings; fatigue and myelosuppression[28]. Knowledge about the toxicities that most affect the patients' quality of life is of paramount importance for the healthcare team and has been considered a key factor in clinical decision-making[31].

In this study, alopecia, asthenia, paresthesia and neutropenia were the toxicities recorded with the highest degree of severity. The results are similar to those found in other publications[12-13]. The growing knowledge of the healthcare teams about the undesirable effects associated with the use of the CP regimen has contributed for healthcare professionals to adopt strategies that seek to minimize the negative effects of the therapy. For example, to prevent neurotoxicities, healthcare teams have adopted in clinical practice the use of detoxifying agents (amifostine, sodium tiosulfate), nerve growth factor stimulants (retinoic acid), antioxidants (vitamin E), electrolytes, chelators, ion channel modulators, antiepileptic agents and corticosteroids[32]. In cases of sarcopenia, associated with disease progression, dose reduction has been a strategy used to minimize the toxicity of cytotoxic agents[33]. Despite the promising results of these strategies, there is still no structured algorithm to prevent toxicity in patients using the CP regimen in the clinical practice. There are still many inconclusive clinical results on the risk factors involved in toxicities, considering both defined (body composition, for example)[33-34] and non-definite (genetic polymorphism)[14,35-36] individual variables.

As a way to prevent the occurrence of the toxicities identified in this study and intervene negatively in the treatment of women with ovarian cancer, the scientific literature has highlighted the importance of multiprofessional action, including pharmaceutical professionals in the follow-up of cancer patients, contributing both to the prevention and resolution of toxicities and other drug-related problems, and to improving the quality of life of individuals undergoing treatment[37-38]. However, these studies are still few. Therefore, there is ample opportunity to conduct future research studies aimed at identifying the effects and impacts of pharmacists' performance on clinical outcomes in ovarian cancer patients.

The use of the CP regimen for six cycles is still widely accepted as the standard first line of treatment, considering its results in overall survival[39], despite recent advances in the treatment of ovarian cancer with the use of targeted therapies, such as antiangiogenic and PARP (poly ADP-ribose polymerase) inhibitors[11]. From this perspective, the adoption of clinical interventions that seek to minimize toxicity effects, such as dose reduction, may not be sufficient to control them, predicting an early change or suspension of treatment[40]. This fact was observed in seven of the patients analyzed in this study. The incorporation of strategies that can prevent the occurrence of toxicities is a necessity, because it favors the effectiveness of therapy and promotes greater patient safety. Oneda *et al*.[40], for example, propose adopting hilotherapy during chemotherapy infusion to prevent the onset of peripheral neuropathy associated with the CP regimen. However, studies focusing on identifyin strategies to prevent cancer treatment-related toxicities are still rare.

As a limitation of the study, it is noted that data collection conducted retrospectively and through analysis of medical records may be subjected to information-related gaps and under-recording. To minimize such effects, we sought to adopt multiple sources of information. The lack of knowledge about drugs acquired by patients outside the studied institution or used through self-medication can also be considered as another limitation. However, it is considered that this effect on the results found would be minimal, since all drugs prescribed and supplied by the institution were considered. However, we cannot rule out the occurrence of other drug interactions. Even so, it is considered that the study contributed to fill a scientific gap by describing the pharmacotherapeutic profile and possible risk factors related to the occurrence of toxicities in Brazilian patients using the CP regimen, since studies with real-world data in this population are still few.

Conclusion

The study allowed us to identify the main toxicities, their respective levels of severity, potential associated risk factors, and clinical interventions adopted by the healthcare teams, affecting ovarian cancer patients treated with the CP regimen in a specialized oncology hospital in Rio de Janeiro, Brazil.

In addition, the results found have the potential to help healthcare professionals in taking preventive measures and controlling possible toxicities, as they can compromise quality of life and treatment outcomes.

It is noted that by identifying the clinical and pharmacotherapeutic profiles, and the identification of toxicities in patients, it is possible to improve effectiveness of treatment with the CP regimen and the safety of women with ovarian cancer who undergo this treatment.

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Collaborators

TAG and MJSS contributed to design of the project, data analysis and interpretation, and in writing of the article; GVC contributed to design of the project, data analysis and relevant critical review of the intellectual content. All the authors approved the final version to be published and assume responsibility for all information included in the paper, ensuring accuracy and integrity of any of its parts.

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Declaração de conflito de interesses

Os autores declaram inexistência de conflitos de interesses em relação a este artigo.

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