Evaluation of the Clinical Profile of Patients with Gynecological Tumors undergoing Antineoplastic Treatment

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Avaliação do Perfil Clínico de Pacientes com Tumores Ginecológicos em Tratamento Antineoplásico

Evaluación del Perfil Clinico de Pacientes con Tumores Ginecológicos Sometidos a Tratamiento Antineoplásico

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ABSTRACT

Introduction: The evaluation of the causes of interruption of the antineoplastic therapeutic plan allows the development of strategies that increase adherence and positive treatment outcomes. **Objective:** Outline the clinical profile of the patients with gynecological tumors under intravenous antineoplastic treatment, identifying the risk of interrupting the therapeutic plan. **Method:** Retrospective and quantitative study (2011-2018), including patients older than 18 years old, with gynecological tumors undergoing antineoplastic treatment. The database was built from the spreadsheets of antineoplastic drug handling at the Chemotherapy Center. The variables collected were: year of treatment, age, type of tumor, purpose of treatment, protocol, medication, dose, start and end of treatment, and treatment interruption. **Results:** 6,496 patients over 8 years were evaluated. Fifty two percent of the patients presented cervical cancer. Almost forty eight percent (47.6%) showed a palliative treatment purpose for their tumors. Approximately, twenty three percent (22.6%) interrupted the antineoplastic treatment. For adjuvant, curative, and palliative purposes the age range 18-30 presented the highest interruption, respectively 33%, 36% and 41%. The paclitaxel/carboplatin protocol was the most prescribed with a significant percentage of interruption. **Conclusion:** The findings suggest that there is an association between treatment discontinuation and patients' age and therapeutic purpose.

Key words: genital neoplasms, female; drug-related side effects and adverse reactions; antineoplastic agents; withholding treatment.

RESUMO

Introdução: A avaliação das causas de interrupção do plano terapêutico antineoplásico permite a elaboração de estratégias que aumentem a adesão e os desfechos positivos do tratamento. **Objetivo:** Traçar o perfil clínico das pacientes com tumores ginecológicos, em tratamento antineoplásico intravenoso, identificando o risco de interrupção do plano terapêutico. **Método:** Estudo retrospectivo e quantitativo (2011-2018), incluindo pacientes maiores de 18 anos, com tumores ginecológicos em tratamento antineoplásico. O banco de dados foi construído a partir das planilhas de controle de antineoplásicos da Central de Quimioterapia. As variáveis coletadas foram ano de tratamento, idade, tipo de tumor, finalidade do tratamento, protocolo, medicamento, dose, início e término do tratamento e interrupção do tratamento. **Resultados:** Avaliaram-se 6.496 pacientes ao longo de oito anos. Cinquenta e dois por cento das pacientes apresentavam câncer cervical. Quase 48% (47,6%) apresentaram uma finalidade de tratamento paliativo para seus tumores. Aproximadamente 23% (22,6%) interromperam o tratamento antineoplásico. Para fins adjuvantes, curativos e paliativos, a faixa etária de 18 a 30 anos apresentou a maior interrupção, respectivamente 33%, 36% e 41%. O protocolo paclitaxel/carboplatina foi o mais prescrito com percentual significativo de interrupção. **Conclusão**: Os achados sugerem que exista uma associação entre a suspensão do tratamento e a idade dos pacientes e a finalidade terapêutica.

Palavras-chave: neoplasias dos genitais femininos; efeitos colaterais e reações adversas relacionados a medicamentos; antineoplásicos; suspensão de tratamento.

RESUMEN

Introducción: La evaluación de las causas de interrupción del plan terapéutico antineoplásico permite el desarrollo de estrategias que aumentan la adherencia y los resultados positivos del tratamiento. **Objetivo**: Delinear el perfil clínico de las pacientes con tumores ginecológicos, en tratamiento antineoplásico intravenoso, identificando el riesgo de interrupción del plan terapéutico. **Método**: Estudio retrospectivo y cuantitativo (2011-2018), que incluyó a pacientes mayores de 18 años, con tumores ginecológicos en tratamiento antineoplásico. La base de datos se construyó a partir de las hojas de cálculo del manejo de fármacos antineoplásicos en el Centro de Quimioterapia. Las variables recogidas fueron: año de tratamiento, edad, tipo de tumor, finalidad del tratamiento, protocolo, medicación, dosis, inicio y finalización del tratamiento e interrupción del mismo. **Resultados**: Se evaluaron 6.496 pacientes durante los ocho años. El 52% de las pacientes presentó cáncer de cuello uterino. Casi el 48% (47,6%) mostró un propósito de tratamiento paliativo para sus tumores. Aproximadamente, el 23% (22,6%) interrumpió el tratamiento antineoplásico. Para fines adyuvantes, curativos y paliativos, el rango de edad de 18 a 30 años presentó la mayor interrupción, respectivamente 33%, 36% y 41%. El paclitaxel/carboplatino fue el más prescrito con un porcentaje significativo de interrupción. **Conclusión**: Nuestros hallazgos sugieren que existe una asociación entre la interrupción del tratamiento y la edad de los pacientes y el propósito terapéutico.

Palabras clave: neoplasias de los genitales femeninos; efectos colaterales y reacciones adversas relacionados con medicamentos; antineoplásico; privación de tratamiento.

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INTRODUCTION

According to Siegel et al.[1], cancer is the second cause of death and the major public health issue in the world. Gynecological cancers are among the 10 cancers that most affect women worldwide with considerable mortality[2,3]. In relation to their types, it has been mainly affecting cervix, ovary, endometrium (body of the uterus), vulva and vagina, but it can also occur in embryonic attachments, like placenta, as gestational trophoblastic neoplasia[4-8].

Gynecological tumors have different histological subtypes requiring distinct treatment and management modalities, commonly surgery and chemotherapy. Chemotherapy may precede surgery (neoadjuvant), administered after surgery (adjuvant) or palliative. Radiotherapy and brachytherapy are also typically used in combination with the antineoplastics treatment[5-8]. All treatment strategies have certain degree of risk and could be harmful to the patient. Antineoplastic drugs have been used in chemotherapy treatment and, due to its toxicity, may cause adverse drug reactions (ADRs) in different degrees, occurring during drug infusion and later[9].

Antineoplastic treatment can present toxicities, which can cause its temporary or permanent interruption, requiring a reassessment of the therapeutic plan. Cytopenia, such as neutropenia and thrombocytopenia, is an important cause for treatment interruption, especially febrile neutropenia[10-12]. Other factors that may affect the continuity of the antineoplastic treatment are decline of patient performance status, advanced age, prolonged hospitalizations and extensive disease[11,12].

By calculating the interruption rate of antineoplastic treatment protocols, it is possible to identify profiles with greater susceptibility to discontinuation, and to propose strategies for better adequacy of the therapeutic plans.

There are some studies in literature addressing treatment interruption rates as seen in Won et al.[13] (54.6%), Woopen et al.[14] (38.5%), Wildes et al.[15] (26.2%), Aaldriks et al.[16] (28.5%), Kalsi et al.[17] (15.7%) and Extermann et al.[18] (50.9%). However, they differ from each other due to the number of patients and tumor types. These studies involved other than gynecological tumors.

In the scope of gynecological tumors, no findings relating clinical data of these tumors in the Brazilian population with the susceptibility to interrupt therapeutic plans were found, demonstrating the relevance of the findings of the current study.

This study aimed to outline the clinical profile of the patients with gynecological tumors receiving intravenous antineoplastic treatment and identify the risk of interrupting the therapeutic plan.

METHOD

Study design

Retrospective and quantitative study conducted from 2011 to 2018 at the Chemotherapy Center of the Cancer Hospital II of the National Cancer Institute José Alencar Gomes da Silva, a treatment unit of the public health system specialized in gynecological cancer.

Patient selection and data collection

The study included patients older than 18 years with gynecological tumors undergoing antineoplastic treatment from 2011 to 2018. Patients enrolled in clinical research protocols were excluded, since the interruption of the treatment is assessed according to the specific protocol.

The database was built from the data entered at spreadsheets of antineoplastic drug handling at the Chemotherapy Center. The variables analyzed were: year of treatment, patient age, type of tumor, purpose of treatment (curative, neoadjuvant, adjuvant and palliative), protocol, medication and dose.

The analysis of treatment interruption was based on the number of protocol cycles prescribed and treatment visit dates.

In order to determine the absolute and relative frequencies of tumor types, gynecological tumors of the Endometrium (Uterus, Endometrium and Body of the Uterus), Gestational Trophoblastic (placenta, hydatidiform mole and choriocarcinoma), Cervical (Cervical, Vagina and Vulva) and Ovarian were considered.

The Institutional Review Board of INCA approved the study, number 3.451.467, which collected and utilized data from the Pharmacy Service routine.

Statistical analysis

Descriptive statistics was performed for the variables: age, type of tumor, treatment purpose, protocol, and treatment conclusion. The influence of these variables on treatment interruption was tested using the chi square test, which evaluates the dependence between categorical variables.

With SPSS and Microsoft Excel, it was possible to analyze the antineoplastic infusion dates, identifying the treatment interruption. Statistical analyses were completed using IBM SPSS 22.0 (IBM Co., Ar-monk, NY, USA) and $p<0.05$ was considered significant.

RESULTS

6,496 patients over 8 years were evaluated, with mean of 815 (920-736) per year. The clinical and therapeutic characteristics of these patients are summarized in Table 1.

Table 1. Clinical and Therapeutic Characteristics of the patients under treatment in the Chemotherapy Center of the Cancer Hospital II (HCII)

Clinical characteristics (n=6,496)		
Cancer site	**n**	**%**
Cervical	**3,401**	**52%**
Ovarian	1,91	29%
Endometrium (body of the uterus)	1,057	16%
Gestational trophoblastic	129	2%
Treatment status		
Treatment interrupted	**1,482**	**22.8%**
Treatment completed	5,015	77.2%
Treatment purpose		
Palliative	**3,095**	**47.6%**
Neoadjuvant	1,946	30%
Adjuvant	1,146	18%
Curative	310	5%

Fifty two percent of the patients had cervical tumors, and 29.4%, ovarian cancer. 97.8% were treated on an outpatient basis, and 2.2% on an inpatient basis. 47.6% of the cases were palliative treatment. Furthermore, 22.6% of the patients interrupted the antineoplastic treatment.

This study described that gynecological tumors affect middle-aged older women (51 – 70 years old) mainly, with an incidence of 49.6% (3,221 women). However, the incidence in the youngest women was also high 38.1% (2,472 women, 18 – 50 years old).

Table 2 shows the treatment interruption by purpose and age range, presenting a reality other than the hypothesis adopted. For adjuvant, curative and palliative purposes, the age range of 18 – 30 years had the highest interruption rate, 33%, 36% and 41%, respectively. For neoadjuvant purpose, the age range with highest interruption was 51 – 70, with 21%. Apart from curative purposes, the association between age, treatment purpose and interruption was significant.

Table 3 presents the association between treatment interruption by purpose and tumor type. This association was significant for cervical, endometrial and ovarian tumors. For cervical cancer, palliative and adjuvant purposes had the highest interruption rates, respectively 31% and 29%. Endometrial tumors presented rates of 27% for neoadjuvant and palliative purposes. Ovarian tumors showed the highest rates for curative purpose (45%). For gestational trophoblastic neoplasia, the highest rates were curative and palliative purposes, respectively, 31% and 75%, however, it presents statistical bias due to the low incidence of the palliative purpose.

The main reasons for discontinuing treatment, in order of incidence, were: toxicity, disease progression, worsening performance status, referral to the exclusive palliative care unit, lack of adherence to treatment and

Table 2. Association between treatment interruption by treatment purpose and age range. $p<0.05$ was considered significant

Interruption by age and treatment purpose (n=6,496)							
Treatment purpose	**Age range**	**Treatment interrupted**		**Treatment completed**		**Total**	***p value***
		n	**%**	**n**	**%**		
Adjuvant	18 - 30	15	33%	29	67%	44	0.011
	31 - 50	41	16%	214	84%	255	
	51 - 70	102	15%	578	85%	679	
	70+	28	17%	139	83%	168	
Curative	18 - 30	31	36%	56	64%	87	0.260
	31 - 50	40	29%	99	71%	140	
	51 - 70	16	21%	59	79%	75	
	70+	2	29%	5	71%	7	
Neoadjuvant	18 - 30	17	14%	103	86%	120	0.007
	31 - 50	136	15%	767	85%	903	
	51 - 70	163	21%	627	79%	790	
	70+	17	13%	116	87%	134	
Palliative	18 - 30	37	41%	53	59%	53	0.041
	31 - 50	241	29%	592	71%	592	
	51 - 70	463	27%	1,224	73%	1,224	
	70+	133	27%	352	73%	352	

death during treatment. During this period, 18.2% (1,179) patients died.

The main protocols recommended for cervical tumors treatment were paclitaxel-combined carboplatin (CARBOTAX) and radiotherapy-combined cisplatin (CDDP + RT). These protocols present, respectively, 29% and 18% of interruption rate, as shown in Table 4. CARBOTAX was a palliative protocol and CDDP + RT was a curative protocol.

CARBOTAX and Doxorubicin monotherapy were the main protocols for endometrial tumors, with respectively, 16% and 38% of interruption.

Ovarian tumors also feature CARBOTAX as one of the major protocols, along with gemcitabine alone. For these protocols, the percentage of interruption was, respectively, 10% and 31%.

The main protocol for gestational trophoblastic neoplasia was methotrexate intramuscularly (MTX IM), with 19% of interruption rate.

Considering the toxicity of antineoplastic treatment as the most frequent cause of interruption, and the widespread use of the protocols CARBOTAX and CDDP + RT, in 2018, 4 carboplatin and 1 cisplatin related adverse reactions were reported.

The dose adjustment of the antineoplastic in relation to the previous cycle was present in most interrupted treatments (62%), and in those that were not interrupted (58%), this result was statistically significant.

DISCUSSION

The literature states that advanced age and other issues, as the decline in hepatic and renal metabolism, deterioration of the performance status, increased frequency of comorbidities in older adults are important factors in treatment interruption[13,14]. Advanced disease and palliative treatment would be other strong related factors[14,15]. The hypothesis adopted in this study is that palliative purpose and older adult patients would have been more likely to discontinue antineoplastic treatment.

Although older adults present higher risk of toxicity due to reduced bone marrow reserve and renal and hepatic clearance capacity[19], young and middle-aged adults are also at risk. The socioeconomic situation and the presence of a support network[20] are crucial for the completion of the chemotherapy treatment in all age groups. Another perspective to be evaluated is the access to antineoplastic treatment[21], especially for persons with poor financial status, which may have influenced the high number of patients in palliative chemotherapy. The difficulty of access, on the other hand, makes people seek oncologic services at a very advanced stage of the disease.

In Table 1, most patients were treated with palliative purpose, almost 50% (47.6%) as observed. We could observe that palliative purpose is targeted to patients with

Table 3. Association between treatment interruption by treatment purpose and tumor type. p<0.05 was considered significant

Interruption by cancer site and treatment purpose (n=6,496)							
Cancer site	**Treatment purpose**	**Treatment interrupted**		**Treatment completed**		**Total**	***p value***
		n	**%**	**n**	**%**		
Cervical	**Adjuvant**	**84**	**29%**	**201**	**71%**	**285**	0.00
	Curative	38	24%	121	76%	159	
	Neoadjuvant	284	18%	1,326	82%	1,610	
	Palliative	**419**	**31%**	**928**	**69%**	**1,346**	
Endometrium (body of uterus)	Adjuvant	48	11%	375	89%	422	0.00
	Neoadjuvant	**10**	**27%**	**27**	**73%**	**37**	
	Palliative	**161**	**27%**	**436**	**73%**	**597**	
Ovarian	Adjuvant	54	12%	384	88%	438	0.00
	Curative	**12**	**45%**	**15**	**55%**	**27**	
	Neoadjuvant	39	13%	259	87%	297	
	Palliative	**291**	**25%**	**856**	**75%**	**1,148**	
Gestational trophoblastic	Adjuvant	0	0%	1	100%	1	0.379
	Curative	**39**	**32%**	**84**	**68%**	**123**	
	Neoadjuvant	0	0%	2	100%	2	
	Palliative	**2**	**75%**	**1**	**25%**	**3**	

Table 4. Association between treatment interruption by protocol* and tumor type. $p<0.05$ was considered significant

Protocol by interruption and cancer site (n=6,390)							
Cancer site	Protocol	Treatment Interrupted		Treatment Concluded		Total	*p value*
		n	%	n	%		
Cervical	ADM	8	57%	6	43%	14	0.0
	CARBO monotherapy	15	65%	8	35%	23	
	CARBOTAX	**358**	**29%**	**868**	**71%**	**1,226**	
	CDDP+RT	**367**	**18%**	**1,656**	**82%**	**2,023**	
	EC	7	54%	6	46%	13	
	TAX	15	65%	8	35%	23	
	TOPO weekly	18	95%	1	5%	19	
Endometrium (body of uterus)	**ADM**	**34**	**38%**	**55**	**62%**	**89**	0.0
	ADM+CDDP	2	25%	6	75%	8	
	CARBO monotherapy	17	49%	18	51%	35	
	CARBOTAX	**142**	**16%**	**724**	**84%**	**866**	
	CDDP+RT	5	23%	17	77%	22	
	IFO monotherapy	6	86%	1	14%	7	
	TAX	7	47%	8	53%	15	
	TOPO weekly	2	40%	3	60%	5	
Ovarian	BEP	37	54%	32	46%	69	0.0
	CARBO monotherapy	43	40%	65	60%	108	
	CARBOTAX	**111**	**10%**	**1,042**	**90%**	**1,153**	
	GEMCITABINE	**92**	**31%**	**203**	**69%**	**295**	
	GEMCITABINE+CARBO	5	16%	26	84%	31	
	TAX	51	39%	79	61%	130	
	TOPO weekly	43	47%	48	53%	91	
Gestational trophoblastic	ACTD	16	100%	1	0%	17	0.0
	EMA-CO	2	12%	15	88%	17	
	MTX IM	**13**	**19%**	**54**	**81%**	**67**	
	TETP	8	53%	7	47%	15	

Captions: *ACTD = Actinomycin; ADM = Doxorubicin; CDDP = Cisplatin; BEP = Blemycin+Etoposide+Cisplatin; CARBO= Carboplatin monotherapy; CARBOTAX= Carboplatin+Paclitaxel; EC = Etoposide+Carboplatin; EMA-CO = Etoposide+Methotrexate+Actinomycin+Cyclophosphamide+Vincristine; IFO = Iphosphamide; IM = Intramuscular; MTX = Methotrexate; RT = Radiotherapy; TAX = Paclitaxel; TETP = Cisplatin+Etoposide+Paclitaxel; TOPO = Topotecan.

Table 5. Association between treatment interruption by dose adjustment. $p<0.05$ was considered significant

Treatment interruption by dose adjustment (n=48,876)					
Dose adjustment	Treatment interrupted		Treatment concluded		*p value*
	n	%	n	%	
Without dose adjustment	2,294	38%	17,784	42%	0.000
With dose adjustment	**3,805**	**62%**	**24,993**	**58%**	
Total	6,099	100%	42,777	100%	

metastatic tumors. The table shows a worrying reality of Brazilian patients, where many of them had metastases, limiting the use of curative therapeutic protocols.

Globally, cervical cancer is the most prevalent gynecological tumor, however the incidence and mortality rates show a decreasing tendency, greatly influenced

by vaccination, screening and early diagnosis policies, especially in developed countries[2]. In this logic, a small portion of women have metastatic tumors of the cervix, requiring palliative treatment in developed countries, probably justifying the shorter survival of these patients due to the absence of standard palliative treatment[22,23].

The second most common type of gynecological tumor, ovarian cancer, does not portray the same reality[2]. Regardless of the population's socioeconomic level, screening methods and early diagnosis are scarce, which explains the diagnosis in advanced stages and the high lethality of this type of tumor[24]. Approximately 70% of the patients with ovarian cancer are diagnosed in advanced stage, requiring palliative treatment through different therapeutic lines[23,24].

The data presented by Renna Junior and Azevedo e Silva[20], from 2000 to 2012 in Brazil, shows that most of the women with cervical cancer were diagnosed at stages III and IV (advanced disease with metastasis), corresponding to palliative antineoplastic treatments.

Renna Junior and Azevedo e Silva[20], like Carvalho et al.[21] in their respective studies, present a significant percentage of patients in advanced stage at the time of diagnosis with definition of the therapeutic plan, which is an aggravating factor, since it limits the possibilities of cure. This is the Brazilian reality about cervical cancer, quite different from what is seen in most parts of the world.

Treatment interruption for tumor types such as cervical, ovarian, and endometrial have been evaluated in some studies such as Li et al.[25] with 40% and Krusun et al.[26] with 18.7% of interruption for cervical cancer. Data from Jang et al.[27] demonstrate that for most patients with ovarian and cervical tumors, palliative chemotherapy was discontinued early, with an average of 3 cycles performed. Woopen et al.[14] found around 38%, Muralikrishnan et al.[28], 19.2%, Chambers et al.[29], 28.1%, and Falandry et al.[30], 26.1% for ovarian cancer. Khouri et al.[31] detected 20% of interruption for endometrial cancer and de Boer et al.[32], around 20%.

Most patients with gynecological cancers are older adults, as shown in Table 2 and data about risk of antineoplastic treatment is found in the literature for this population. This risk is increased due to the greater vulnerability of normal tissues to chemotherapy, resulting in a higher incidence of toxicities that may promote treatment interruption[24]. Therefore, it is possible to notice association between age and treatment interruption for neoadjuvant, adjuvant and palliative purposes. Krusun et al.[26], Woopen et al.[14], Won et al.[13], Wildes et al.[15] and Kalsi et al.[17] have not found any association between age and treatment interruption, unlike Hurria et al.[33].

Contrary to the literature, Table 2 shows a high percentage of interruption of antineoplastic treatment in the age range 18 – 30 years for adjuvant, curative, and palliative purposes. These interruption rates are not expected, since age-related functional decline is not present[23].

A very high range of antineoplastic protocols was not addressed in the scope of the article. While some were used for a few patients and with high rates of interruption, others like CARBOTAX were widely used, with rates not so high, but requiring special attention, mainly due to the risk of toxicity.

de Boer et al.[32] presents the interruption of carboplatin + paclitaxel/cisplatin protocols associated with radiotherapy increased as more cycles were applied, reflecting accumulation of toxicity.

An alternative to treatment interruption due to associated toxicity is dose adjustment/reduction. Won et al.[13], Kalsi et al.[17] and Aaldriks et al.[16] utilized the evaluation of patients who have taken the full dose and the reduced dose in their studies. 62% (n = 33,783) of the interrupted treatments had dose adjustment, indicating that, possibly, these patients had some degree of toxicity in previous cycle, or even alteration of the body surface due to weight gain or loss, and in renal function.

The data corroborate the information from Renna Junior and Azevedo e Silva[20] and Carvalho et al.[21] about public policies gaps for screening and early detection of cervical cancer; therefore, it is possible to infer that it is necessary to rethink the therapeutic plans not only for this tumor, but for gynecological tumors in general, in order to reduce early treatment discontinuation, mainly for young and middle-aged patients. However, it is also necessary to think about strategies for early detection and screening of endometrium and ovary tumors, which, although not easily preventable and traceable like cervix tumor, may have their risk factors modified and detected prior to reaching more advanced stages.

The study has limitations due to its retrospective nature as information bias and the events that occurred in the past. Another difficulty was the access to computerized information because of the long period investigated, unavailability of data of the early years, and evaluation of the outcome of different therapeutic approaches due to sub-notification.

CONCLUSION

The findings suggest that there is an association among treatment discontinuation and tumor type, patients' age and therapeutic purpose, whereas metastatic tumors, middle-aged and older patients in palliative chemotherapy are more likely to discontinue treatment.

Further studies will be needed to identify the factors that contribute to the discontinuity of the proposed treatments as those patient-related, toxicity of antineoplastic agents and/or definition of the therapeutic plan.

A more accurate analysis of treatment interruption by tumor type, age range and treatment line, assessing change between treatment lines, is among the future perspectives, looking for interruption reasons, especially when they are related to toxicity, in order to correlate to the active search for pharmacovigilance realized in our unit.

CONTRIBUTIONS

Priscila Helena Marietto Figueira, Liliana Rosa Alves Manaças, and Ana Paula do Nascimento Antonio designed the study. Ana Paula do Nascimento Antonio collected and analyzed the data and drafted the manuscript. Thiago Ribeiro Nery and Ana Paula do Nascimento Antonio conducted the statistical analyzes. Liliana Rosa Alves Manaças. and Priscila Helena Marietto Figueira supported the data interpretation and Ana Paula do Nascimento Antonio, Liliana Rosa Alves Manaças and Priscila Helena Marietto Figueira supported the drafting of the manuscript.

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CONFLICTS OF INTEREST

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