Research on Cardiotoxicity in Patient Chart Submitted to R-CHOP Chemotherapy: a Case Study

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Pesquisa de Cardiotoxicidade em Prontuário de Paciente Submetido à Quimioterapia R-CHOP: um Estudo de Caso

Investigación de Cardiotoxicidad en Prontuario de Paciente Sometido a la Quimioterapia R-CHOP: un Estudio de Caso

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Abstract

Introduction: Cardiotoxicity is one of the most significant effects of oncological treatment. Among the major relevant consequences, heart failure with systolic or diastolic ventricular dysfunction stands out. **Case report**: 39-year-old female patient with diffuse large B-cell non-Hodgkin's lymphoma who underwent rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP chemotherapy) and presented fatigue while exerting small efforts and increased blood pressure. The echocardiogram showed mild left ventricular dysfunction with diffuse hypokinesia and reduction of left ventricular ejection fraction (LVEF) associated with the possible cardiomyotoxicity of doxorubicin. The case was identified in a chart survey, and analyzed according to the Naranjo Algorithm, and then the severity of the adverse cardiovascular reactions was determined. **Conclusion**: This study highlights the importance of the active search for cardiovascular events in medical charts of patients undergoing cardiotoxic chemotherapy and the role of pharmacovigilance in this context.

Key words: Cardiotoxicity; Doxorubicin/therapeutic use; Pharmacovigilance; Medical Records; Case Reports.

Resumo

Introdução: A cardiotoxicidade é um dos efeitos mais significativos no tratamento oncológico. Entre as implicações mais consideráveis, destaca-se a insuficiência cardíaca com disfunção ventricular sistólica ou diastólica. **Relato do caso**: Paciente do sexo feminino, 39 anos, com linfoma não Hodgkin difuso de grandes células B, submetida à quimioterapia com rituximabe, ciclofosfamida, doxorrubicina, vincristina e prednisona (R-CHOP), que apresentou cansaço aos pequenos esforços e aumento da pressão arterial. O ecocardiograma demonstrou disfunção ventricular esquerda leve com hipocinesia difusa e redução da fração de ejeção do ventrículo esquerdo (FEVE), associadas à possível cardiomiotoxicidade da doxorrubicina. O caso foi identificado em uma pesquisa de prontuário e analisado segundo o algoritmo de Naranjo e, em seguida, foi determinada a gravidade das reações adversas cardiovasculares. **Conclusão**: Este estudo ressalta a importância da busca ativa de eventos cardiovasculares em prontuários de pacientes submetidos à quimioterapia cardiotóxica e do papel da farmacovigilância nesse contexto.

Palavras-chave: Cardiotoxicidade, Doxorrubicina/uso terapêutico; Farmacovigilância; Registros Médicos; Relatos de Casos.

Resumen

Introducción: La cardiotoxicidad es uno de los efectos más significativos del tratamiento oncológico. Entre los efectos más considerables, destaca la insuficiencia cardíaca con disfunción ventricular sistólica o diastólica. **Relato del caso:** Paciente de 39 años con linfoma no Hodgkin difuso de células grandes B que se sometieron a quimioterapia con rituximab, ciclofosfamida, doxorubicina, vincristina y prednisona (R-CHOP). Pequeños esfuerzos y aumento de la presión arterial. El ecocardiograma mostró una disfunción ventricular izquierda leve con hipocinesia difusa y reducción de la fracción de eyección del ventrículo izquierdo (FEVI) asociada con la posible cardiomioxicidad de la doxorrubicina. El caso se identificó en una encuesta gráfica y se analizó de acuerdo con el algoritmo de Naranjo, y luego se determinó la gravedad de las reacciones cardiovasculares adversas. **Conclusión:** Este estudio destaca la importancia de la búsqueda activa de eventos cardiovasculares en los registros médicos de pacientes sometidos a quimioterapia cardiotóxica y el papel de la farmacovigilancia en este contexto.

Palabras clave: Cardiotoxicidad; Doxorubicina/uso terapéutico; Farmacovigilancia; Registros Médicos; Informes de Casos.

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INTRODUCTION

Lymphomas are neoplastic transformations of normal lymphoid cells[1]. They divide morphologically in Hodgkin and non-Hodgkin lymphoma[1]. The most common types of non-Hodgkin lymphoma in adults are the diffuse lymphoma of great cells B, generally aggressive and follicular lymphoma, normally indolent[1-3].

In Brazil, the estimates are 5,370 new cases of non-Hodgkin lymphoma in men and 4,810 in women for each year of 2018-2019[4]. For both genders, it is the 11th neoplasm most common among all types of cancer[1]. These values correspond to an estimated risk of 5.19 new cases for each 100 thousand men and 4.55 new cases for each 100 thousand women[4].

Cardiotoxicity is one of the most significant effects of the oncologic treatment and is responsible for the great morbimortality either acute or chronic[5]. The principal manifestation of cardiotoxicity of oncologic therapies is cardiomyopathy related to the use of anthracyclines (doxorubicin, epirubicin, idarubicin)[6,7]. Studies showed that the systolic dysfunction of the left ventricle (LV) is related to the use of cumulative doses of anthracyclines[8], subsequent administrations can result in permanent injuries either cellular or interstitial that frequently are associated to the risk of development of cardiac insufficiency (CI)[9].

In its acute phase, cardiotoxicity by anthracycline occurs until 14 days after the beginning of the treatment and is rare, transitory and independent of the dose administered[5]. In the chronic phase, it is dose-dependent and can occur in the period of one year or even years after the end of chemotherapy[5]. The most common manifestation of chronic cardiotoxicity is the systolic or diastolic ventricle dysfunction that can result in severe cardiomyopathy with risk of death for the patient[5].

Although there were prior studies, it was not until 2011 the occurred the publication of the First Brazilian Guideline of Cardio-Oncology of the Brazilian Cardiology Society (*I Diretriz Brasileira de Cardio-oncologia da Sociedade Brasileira de Cardiologia)*, where this theme gained more visibility in Brazil[5]. The collaboration and interaction of the disciplines of Cardiology and Oncology have contributed to reduce the cardiovascular adverse effects and pursue better results for the treatment of the patient with cancer[5].

Pharmacovigilance through active search of cardiovascular reactions in patient's charts submitted to chemotherapy treatment collaborates with cardio-oncology about the safety profile of these drugs. There is a national gap of pharmacovigilance studies in this area and the case report represents one case of cardiotoxicity of a patient submitted to therapy with rituximabe, cyclophosphamide, doxorubicin, vincristin and prednisone (R-CHOP), identified in a study of pharmacoepidemiology.

The objective of this article is to describe a case report of a patient submitted to chemotherapy with the protocol R-CHOP, from 2013 to 2018, who presented cardiotoxicity after the use of doxorubicin.

CASE REPORT

Initially, the data were collected from the chart. Next, the patient was interviewed by the pharmacist for complementation of information and signed the Informed Consent Form. The Institutional Review Board approved the study on February 14, 2019, CAAE: 98429018.0.0000.5243.

Female patient, 39 years, brown, cleaning lady, born in Rio de Janeiro, was attended at a Hematology Service of a hospital in the State of Rio de Janeiro. No comorbidity, no history of tobacco addiction or alcoholism, diagnosed with diffuse non-Hodgkin lymphoma of great cells B in the histopathological test in 2015, staging III-B, prior test of normal echocardiogram before the commencement of the treatment, eight cycles of chemotherapy R-CHOP. Reported fatigue while exerting small efforts at the hematology consultation six months after the end of chemotherapy, echocardiography was performed. Presented normal dimensions of the left ventricle, but with initial loss of ellipsoid geometry and mild left ventricle dysfunction with diffuse hypokinesia and without segmental dysfunction. Normal contractile function of the right ventricle. Atrium with normal volumes and dimensions. Ejection fraction of the left ventricle of 45%. The test was repeated 15 days after with color *Doppler* presenting signs of diastolic dysfunction of the left ventricle in staging I with ejection fraction of 70%. Although the physician have reported suspicion that the ventricle dysfunction and the reduction of the ejection fraction were associated to cardio myotoxicity of doxorubicin, the patient did not initiate follow up with cardiologist.

After the event reported, the patient still submitted to 27 sessions of chemotherapy with protocol ifosfamide, carboplatin and etoposide (ICE), and bone marrow transplantation in another healthcare unit with good response to the transplantation and under follow up with hematologist.

The pharmacist interviewed the patient to record suggestive signs or symptoms of cardiotoxicity and reported fatigue in small efforts and increase of blood pressure after chemotherapy.

DISCUSSION

The patient in question had risk factors as her gender, cumulative dose higher than 400 mg/^{m2} and concomitant use of other cardiotoxic chemotherapeutic drug as cyclophosphamide, which was already reported in another study for the development of cardiotoxicity by doxorubicin, 400 mg/m^2, Martins et al.[10] A total dose of doxorubicin equal or higher than 400 mg/m^2 suggests elevated cumulative dose and needs follow up and control[5-7,9,10]. Doxorubicin, like the other anthracyclines presents an incidence of cardiotoxicity (reduction of the left ventricular ejection fraction – LVEF and or CI) of 5% to 35% of the cases and many times, irreversible[5-7,9,10]. In this case, the patient presented left ventricular dysfunction and reduced ejection fraction. This is the result of the injury by doxorubicin under the myocardium[10,11]. The anthracyclines were described initially as irreversible cumulative dose and for causing mitochondrial injury, however, the possibility of reverse remodeling and recovery of the ventricular function exists[10,11]. The patient of this case recovered from LVEF.

After the interview with the pharmacist, the patient was referred to the clinic of cardiac insufficiency to initiate its follow up. The cardiovascular events presented by the patient, as fatigue from small efforts, the increase of the blood pressure and left ventricular dysfunction with reduction of the left ventricular ejection fraction were associated to the use of doxorubicin and submitted to evaluation of causality of suspicion of adverse reaction by the algorithm of Naranjo[12] (Table 1), considering possible adverse reactions (score 4).

In item 5 of the algorithm of Naranjo[12], the alternative cause considered was: the use of other cardiotoxic medication as cyclophosphamide that can lead to reduction of LVEF and/or CI of 2% to 10 % of the cases[13]. The CI for this drug is uncommon (1/1000 a 1/100) and the increase of blood pressure is a very rare reaction for this drug (<10 thousand), this reduces the value of the algorithm, but the reactions for doxorubicin are more common (5% to 35% of the cases)[13].

Next, the determination of the severity of the adverse reactions followed the Guide for Notification of Oncology Adverse Events (*Guia para Notificação de Eventos Adversos em Oncologia*[14]). The reactions were moderate according to the Guide.

Regardless of the frequent use of doxorubicin in many chemotherapy protocols because of its cardiotoxic potential, the follow up and control are mandatory. Measures like administration of lower doses in extended times reducing plasmatic peaks, monitoring of doses higher than 400 mg/m^2 and regular follow up with echocardiogram can contribute to avoid doxorubicin-provoked cardiotoxicity[5].

For patients with cancer and previous hypertension or with development of hypertension after cancer treatment as in the reported case, the recommendation is to adopt the criteria established by the *Eight Joint National Committee*[15] and the recommendations of the I Brazilian Guideline of Cardio-Oncology (*I Diretriz Brasileira de Cardio-Oncologia*[5]). For these groups, the advise is to control and monitor the blood pressure during chemotherapy and prevention of cardiovascular adverse events for the patients who tolerate this treatment[5,15,16].

CONCLUSION

This result shows the importance of the study of cardiovascular reactions in patients in chemotherapy with

Table 1. Determination of the causality of fatigue, ventricle dysfunction and elevation of the blood pressure at the exposure of doxorubicin*

Questions	Yes	No	Unknown	Sum of the scores
1. There are conclusive notifications about these reactions?	+1	0	0	+1
2. Did the reaction appear after the administration of the drug?	+2	-1	0	+2
3. Did the reaction improve when the drug was suspended?	+1	0	0	0
4. Did the reaction resume when it was re-administered?	+2	-1	0	0
5. There are alternative causes (even another drug)?	-1	+2	0	-1
6. The reaction reappears with the introduction of placebo?	-1	+1	0	0
7. Is the plasmatic concentration in its toxic level?	+1	0	0	+1
8. Did the reaction increase with higher dose or reduced with lower dose?	+1	0	0	0
9. Did the patient experienced similar reaction formerly with medications of the same drug?	+1	0	0	0
10. Was the reaction confirmed by any objective evidence?	+1	0	0	+1
		Total		**4**

Note: *Based in the algorithm of Naranjo[12].

doxorubicin and the regular evaluation of cumulative doses. Pharmacovigilance had a key role in the active search and application of the algorithm, for the determination of the causality of adverse reactions and collaborated for the studies of cardio-oncology and drugs monitoring In addition, the echocardiogram is quite relevant to monitor these patients to ensure an earlier cardiologic monitoring.

CONTRIBUTIONS

Patricia Marques Soares Valente, Wolney de Andrade Martins and Selma Rodrigues de Castilho contributed substantially for the conception, planning, analysis and interpretation of data, wording, critical review and elaboration of the final version.

Eduardo Pinho Braga, Thamires Lopes da Silva, Thamires Ferreira Neves and Walter Claudino Pires de Souza contributed substantially for the analysis and interpretation of the data. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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