ACTA 30 YEARS 1988 - 2018

Original Article

Peripheral neuropathy in people with multiple myeloma

Neuropatia periférica em pessoas com mieloma múltiplo

Neuropatía periférica en personas con mieloma múltiple

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Keywords
Multiple myeloma; Neurotoxicity syndromes; Neurologic manifestations; Drug therapy, combination; Antineoplastic agents

Descritores
Mieloma múltiplo; Síndromes neurotóxicas; Manifestações neurológicas; Quimioterapia combinada; Antineoplásicos

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Submitted
June 13, 2018

Accepted
August 20, 2018

Abstract

Objective: To investigate the prevalence and incidence of peripheral neuropathy (PN) related to antineoplastic therapy in people with multiple myeloma and the association between chemotherapy regimens and peripheral neuropathy after treatment.
Method: This is a documentary and correlational study carried out in two reference sites for cancer treatment, located in the Brazilian states of Ceará and Minas Gerais, with an analysis of patients treated between January 2013 and January 2016. A descriptive and inferential analysis of data was carried out by means of chi-square and Fischer's exact tests.
Results: The study assessed 100 medical records of people with multiple myeloma, who were aged 62.7 years on average and were mostly men (64%). The most used chemotherapy regimen (60%) was bortezomib, dexamethasone, and cyclophosphamide; 20% of patients had peripheral neuropathy before treatment, 68% had it during treatment and 56% at the end of treatment. There was no association between chemotherapy regimens and peripheral neuropathy after treatment.
Conclusion: Our study showed an increase in the incidence of PN in individuals undergoing treatment of multiple myeloma, 80% had symptoms of neuropathy before and/or during and/or after treatment with chemotherapy regimens. Predominance was of elderly retired men. The most common chemotherapy regimen was bortezomib/dexamethasone/cyclophosphamide and there was no association between regimens used and PN after treatment. The implications of these observations rest on the need for a permanent assessment of PN in people with multiple myeloma, in addition to a strict follow-up to this event in the course of treatment and after it, as well as the management of adverse events and alterations related to the disease. There was no association between chemotherapy regimens and peripheral neuropathy after treatment. It is expected that the results obtained help in the organization of a data record about PN in patients with cancer, with the main purpose of establishing targets of intervention, thus making care more efficient and comprehensive.

Resumo

Objetivo: Investigar a prevalência e incidência de neuropatia periférica relacionada ao tratamento com antineoplásicos de pessoas com mieloma múltiplo bem como a associação entre os esquemas quimioterápicos e a neuropatia periférica após o tratamento.
Método: Estudo documental, correlacional, realizado em dois locais de referência para tratamento oncológico, localizados nos estados do Ceará e Minas Gerais, com análise de pacientes atendidos entre janeiro/2013 e janeiro/2016. Os dados foram analisados utilizando-se análise descritiva e inferencial a partir dos testes qui-quadrado e exato de fisher.
Resultados: Foram avaliados 100 prontuários de pessoas com mieloma múltiplo com média de idade de 62,7 anos, maioria de homens (64%). O esquema quimioterápico mais utilizado (60%) foi o bortezomibe, dexametasona e ciclofosfamida; 20% dos pacientes apresentavam neuropatia periférica antes do tratamento, 68% desenvolveram durante o tratamento e 56% ao finalizar o tratamento. Não houve associação entre os esquemas quimioterápicos e a neuropatia periférica após o tratamento.
Conclusão: O presente estudo mostrou um aumento da incidência de NP em indivíduos em tratamento para o MM, 80% apresentaram sintomas de neuropatia antes e/ou durante e/ou após o tratamento com esquemas quimioterápicos. A predominância foi de homens idosos aposentados. O esquema quimioterápico mais utilizado foi o VDC e não foi identificada associação entre os esquemas utilizados e a NP após término o tratamento. As implicações dessas observações recaem sobre a necessidade de avaliação contínua da NP em pessoas com MM, além da monitorização rigorosa desse evento no decorrer do tratamento e após o mesmo, bem como o manejo dos eventos adversos e alterações relacionadas a doença. Não houve associação entre os esquemas quimioterápicos e a neuropatia periférica após o tratamento. Espera-se que os resultados obtidos auxiliem na organização de um registro de dados sobre NP em pacientes com câncer, com o objetivo principal de determinar alvos de intervenção, tornando o cuidado mais eficiente e integral.

Resumen

Objetivo: investigar la prevalencia e incidencia de la neuropatía periférica relacionada al tratamiento con antineoplásicos de personas con mieloma múltiple, así como la asociación entre los regímenes de quimioterapia y neuropatía periférica después de tratamiento.
Método: Estudio documental, correlativo, realizado en dos puntos de referencia para el tratamiento del cáncer, los cuales se encuentran en los estados de Ceará y Minas Gerais, con análisis de pacientes tratados entre enero / 2013 y enero / 2016. Los datos fueron analizados utilizando el análisis descriptivo e inferencial a partir de las pruebas qui-cuadrado y exacto de Fisher.
Resultados: Fueron evaluados 100 expedientes de personas con mieloma múltiple con una edad media de 62,7 años, siendo la mayoría hombres (64%). El esquema quimioterápico más utilizado (60%) fue el bortezomib, dexametasona y ciclofosfamida; el 20% de los pacientes presentaban neuropatía periférica antes del tratamiento, el 68% la desarrolló durante el tratamiento y el 56% al finalizar el tratamiento. No hubo asociación entre los esquemas quimioterápicos y la neuropatía periférica después del tratamiento.
Conclusión: Este estudio mostró una mayor incidencia de NP en individuos que reciben tratamiento para MM, el 80% presentó síntomas de neuropatía antes y / o durante y / o después del tratamiento con regímenes de quimioterapia. La predominancia fue de hombres ancianos jubilados. El esquema quimioterápico más utilizado fue el VDC y no se identificó asociación entre los esquemas utilizados y la NP después de terminar el tratamiento. Las implicaciones de estas observaciones recaen sobre la necesidad de evaluación continua de la NP en personas con MM, además del monitoreo riguroso de dicho evento durante el tratamiento y después del mismo, así como el manejo de los eventos adversos y alteraciones relacionadas con la enfermedad. No hubo asociación entre los esquemas quimioterápicos y la neuropatía periférica después del tratamiento. Se espera que los resultados obtenidos ayuden en la organización de un registro de datos sobre NP en pacientes con cáncer, con el objetivo principal de determinar metas de intervención, obteniendo una atención más eficiente e integral.

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DOI
http://dx.doi.org/10.1590/1982-0194201800061

How to cite:
Moreira MM, Rodrigues AB, Oliveira PP, Aguiar MI, Cunha GH, Pinto RM, et al. Peripheral neuropathy in people with multiple myeloma Acta Paul Enferm. 2018;31(4):439-45.

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Conflicts of interest: there are no conflicts of interest to declare.

Introduction

Multiple myeloma (MM) refers to a malignant neoplasia of hematopoietic nature and corresponds to over 10% of hematologic cancer in the world, with an incidence of 2% in people aged under 40.[1,2]

Progress in antineoplastic chemotherapy and hematopoietic stem cell transplantation (HSCT) improved survival rate, but MM remains incurable. People with MM usually develop bone lesions, hypercalcemia, anemia, immunosuppression and renal impairment, accompanied by fatigue, bone pain and peripheral neuropathy (PN). The objectives of these therapies are to control the disease, ensure remission and maximize quality of life.[2-4]

Peripheral neuropathy is one of the most common complications in patients with MM who are undergoing treatment, and it may occur as an aspect of the disease in recently diagnosed individuals (1% to 20%) or as an adverse effect of the chosen treatment (37% to 83%).[5] Risk factors for PN include treatment-specific characteristics, such as drugs, duration, cumulative dose, use of other drugs with a neurotoxic potential such as bortezomib, thalidomide, and cyclophosphamide, in addition to patient-specific factors such as age and comorbidities.[1,6-8] It is worth highlighting that chemotherapy regimens to treat this disease are prescribed according to a staging system and more than half of them include bortezomib.[1,9-11]

Peripheral neuropathy appears with sensory symptoms such as burning dysesthesia, paresthesia, hyperesthesia, and pain. Despite being less common, motor alterations may also occur.[11] It can be scaled according to the sensory and motor neuropathy changes. In the first degree, patients are asymptomatic or lose deep reflexes or present paresthesia, which does not affect the function and, in motor neuropathy, it is asymptomatic; keeping the drug dosage is recommended. In the second degree, symptoms are moderate and affect activities of daily living (ADLs); reducing the drug dosage is recommended. In the third degree, symptoms are severe and hinder ADLs; suspending treatment until symptomatology is improved is recommended, and at the follow-up visit, the dosage is reduced. In the fourth degree, neuropathy is disabling, and treatment interruption is recommended.[12]

The presence of PN has a great impact not only on quality of life, but also on the disease evolution and overall survival, since its treatment very often means reducing or interrupting the drug dosage.[8] Nurses play a key role in the care of patients with risk of PN, including carrying out an initial and continuous assessment, during and after treatment, teaching patients, and making a safe administration of antineoplastics, symptom management and timely consultation of other members of the interdisciplinary team.[8]

There are great challenges in the confirmation and management of PN symptoms, which are associated with a lack of evidence-based practice for symptom management and little understanding of its pathogenesis.[13] Consequently, the question is: What is the prevalence of PN and its incidence during and after treatment with chemotherapy drugs in people with MM? Is there an association between chemotherapy regimens and PN? What are the clinical/sociodemographic/therapeutic aspects of these individuals?

There are few international studies on the topic and in Brazil there are no publications which assess the association between chemotherapy regimens and PN in patients with MM, performed by nurses and whether these professionals evaluate, on a daily basis, signs and symptoms of neuropathic pain and/or sensory or motor PN, and perform a neurological examination.

Therefore, this study is relevant, since PN examination in people with MM in two reference cancer services located in different regions of Brazil will help to document outcomes and define targets for intervention, which will allow for the adoption of a new model to guide clinical practice.

In view of this, the objective of this study was to investigate the prevalence and incidence of peripheral neuropathy related to antineoplastic therapy in people with multiple myeloma and the association between chemotherapy regimens and peripheral neuropathy after therapy.

Methods

This is a quantitative study of documentary nature, carried out in a high-complexity cancer care center

(CACON) located in Ceará and in a large hospital defined as a high-complexity cancer care unit (UNACON), with hematology and teletherapy services in Minas Gerais.

Using convenience sampling, the selection criterion was: medical records of patients with MM confirmed by histopathological/cytological examination, cared for in one of the chosen institutions, from January 2013 to January 2016. This period corresponds to the time when a form based on *Common Terminology Criteria for Adverse Events* v 4.0[14] was applied to all cancer patients with risk factors for neuropathy, in both institutions, in addition to a neurological examination and items for the assessment of signs and symptoms of neuropathic pain and/or sensory or motor PN.

The inclusion criteria were: patients aged over 18 years, who underwent chemotherapy, with medical records properly filled in, and from which essential information about PN could be obtained, such as: signs and symptoms of neurotoxicity, antineoplastic regimen, dosage used, treatment cycle, and PN degree. As for the exclusion criteria: medical records of MM patients without sociodemographic and clinical data, and PN assessment before, during and after treatment.

Medical records were excluded because they were not properly filled in (1), not found in the medical case file service (3) or whose patients had died (12). Therefore, the total sample had 100 medical records.

Data collection was carried out by means of an instrument created by the authors, which addressed sociodemographic variables (age, gender, marital status, origin, education, professional status, and religion); and clinical and therapeutic variables (comorbidities, main complaint at the first visit, staging, types of treatment, chemotherapy regimen performed, evaluation and PN degree).

It is worth noting that this instrument was assessed by six judges as to the relevance, clarity, and applicability of its topics. These professionals had to be experts in the field and their profiles had to meet the following criteria: being a nurse with proven work on Plataforma Lattes (a database of the National Council of Scientific and Technological Development) in the oncology field for at least ten years, having a graduate degree (*strictu sensu*) and having published an oncology paper in the last three years. The judges were required to point out suggestions of items and changes they considered relevant.

Data were processed and analyzed by means of the Statistical Package for the Social Sciences, version 21.0 for Windows®. Double data entry was used for validation. Results obtained for explanatory variables (sociodemographic/clinical/therapeutic) were analyzed by descriptive statistics and; for the association between chemotherapy regimens and the development of PN after treatment, chi-square test and Fischer's exact test were performed, with a significance level of 5%.

The ethical requirements established in Resolution 466/2012 of the National Health Council were met, and the study was approved by the Human Research Ethics Committee of both institutions, under protocol numbers 1.397.337 and 2.083.066.

Results

One hundred medical records were assessed, 25 from a reference cancer treatment institution and 75 from another cancer treatment institution. The average age of participants was 62.7 years (standard deviation of 9.5), ranging from 45 and 81 years, and 64% of them were men. Most of them were married or in an unmarried union (84%), followed by single (6%), widowed (5%) and separated/divorced individuals (5%). With regard to their origin, 89% of individuals lived in an urban area and 11% in a rural area. As for religion, 98% of patients stated that they practiced a religion.

The average level of education of participants was 5.8 years (standard deviation of 4.3), ranging from zero to 17 years. Regarding their professional situation, 52% of patients were retired, 21% were active independent workers, 11% received a retirement pension and kept an informal job, 10% were homemakers and 6% received a disability benefit.

With regard to the presence of comorbidities, 72% of patients had some chronic disease such as

systemic arterial hypertension (SAH) and diabetes mellitus (DM), 24% of which were undergoing a SAH treatment; 10% had some kind of heart disease; hypothyroidism (4%); sequelae of brain stroke (3%); chronic renal failure (2%); and prostate cancer (1%). Bone pain (76%) was the main complaint of patients during the first medical visit, followed by pathological fractures (12%) and asthenia (12%).

Staging of patients with MM, according to the International Staging System (ISS)[2] was 36% at stage I, 34% at stage II and 30% at stage III, at the time of diagnosis. Regarding the types of treatment performed for MM, 56% underwent teletherapy and chemotherapy simultaneously, 24% underwent chemotherapy only, and 20% had an autologous HSCT.

As for the chemotherapy regimen performed, VDC (bortezomib/dexamethasone/cyclophosphamide) was the most prevalent (60%); followed by MPT (melphalan/prednisone/thalidomide) (20%); CTD (cyclophosphamide/thalidomide/dexamethasone) (12%); and VMP (bortezomib/melphalan/prednisone) (8%).

Figure 1 shows the prevalence of PN before (20%) and the incidence during (68%) and at the end of treatment (56%), with chemotherapy regimens of people with MM.

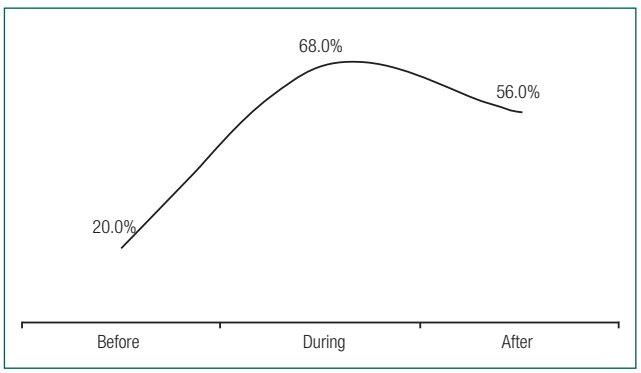

Figure 1. Presence of peripheral neuropathy before, during and after treatment with chemotherapy regimens for the treatment of multiple myeloma between 2013 and 2016 (n=100)

Regarding the degree of changes in sensory and motor neuropathy, 45% of individuals with MM were in the first degree (asymptomatic or loss of deep reflexes or paresthesia, not affecting the function), 30% were in the second degree, that is, with ADL to some extent; 15% in the third degree (severe symptoms, with a limitation in self-care and hindering individuals from performing ADL), and 10% in the fourth degree, with urgent intervention needed. The following neuropathy symptoms were described in the medical records of individuals with MM: paresthesia, dysesthesia, numbness, tingling, neuropathic pain, and loss of balance.

Results of the chi-square test and Fischer's exact test showed that there was no statistically significant difference between chemotherapy regimens and the presence of PN after treatment (Table 1).

Table 1. Association between chemotherapy regimen and peripheral neuropathy after treatment of patients with multiple myeloma between 2013 and 2016 (n=100)

Chemotherapy regimen	Peripheral neuropathy No n(%)	Peripheral neuropathy Yes n(%)	*p-value*
CTD*	5(42.5)	7(57.5)	0.593§
MPT†	10(50.0)	10(50.0)	0.548¶
VMP‡	3(36.5)	5(63.5)	0.543§
VDC	25(41.5)	35(58.5)	0.478¶

*CTD - cyclophosphamide/thalidomide/dexamethasone; †MPT - melphalan/prednisone/thalidomide; ‡VMP - bortezomib/melphalan/prednisone; VDC - bortezomib/dexamethasone/cyclophosphamide; §Fischer's exact test; ¶chi-square test

Discussion

The medical records of individuals with MM treated with chemotherapy regimens were mostly from men who were retired, aged 62.7 years in average, which is in line with data found in the literature.[15-17] The best known epidemiological characteristics of MM include a higher incidence in elderly men over 60 years old.[15] Findings regarding marital status, employment status, level of education, and comorbidities are also in line with previous studies.[2,11,18]

In this study, 40% of individuals had been treated for SAH; a study carried out in the United States with 2,587 patients with advanced MM which aimed to analyze the risks of adverse effects associated with treatments of MM in elderly people found that patients with SAH, PN, thromboembolic events, and heart diseases had a significantly higher risk of developing some toxicity in 6 to 12 months after the beginning of treatment..[19] These data are worrying and confirm the results of this work, since the prevalence of PN before the begin-

ning of treatment (20%) and the incidence during and after treatment nearly tripled.

It is worth noting that discontinuation of drugs that trigger PN, due to the end of treatment protocol, results in the suppression of symptoms, however, toxicity indicators remain to be seen and the existence of permanent lesions must be checked.[4,6,8]

Therefore, nurses need to carry out a comprehensive examination of individuals with MM in order to identify vulnerabilities and problems of patients/relatives and propose assertive and evidence-based interventions since this is the only way to effectively control symptoms, and consequently increase quality of life.[4] Oncology nurses play a key role in the provision of information to patients/families aiming at reducing treatment abandonment, which requires communication skills, observation, counseling, teaching, and management of complex tasks.[20]

Hematology/oncology nurses provide information, education, and support to patients/families with MM, and this has a significant effect on people's experience regarding care; they are also responsible for the continuity of service within the multidisciplinary team and being the link between primary and secondary care services. It is worth noting that the continuous assessment of these individuals is essential for the management of toxicities related to treatment and maintenance of good quality of life.[4,20]

As for religion, 98% of patients stated that they practice a religion. Religious beliefs expressed by means of prayers, meditation and rituals are part of common mechanisms which individuals rely on when they are ill.[21] The more severe the disease, the stronger the relationship with religion, being influenced by the individual's beliefs and values.[22] Faith/spirituality are usually coping strategies used by individuals with cancer. Belief in a superior strength and optimism are positive influences in the development of adaptive responses to difficult times resulting from sickness.[21,22]

With regard to staging, most patients were in stage II and III (64%) in the first visit, which means the disease is advanced. The same finding was pointed out in a cohort study with Chinese patients, in which most of them were undergoing chemotherapy and were at stage II and III, according to the ISS system; a statistically significant association between staging and prognosis, which are inversely proportional, was also observed.[11]

It should be added that when PN results from antineoplastic chemotherapy, it is called chemotherapy-induced peripheral neuropathy (CIPN).

In this study, 55% of individuals with MM had symptoms of motor and sensory neuropathy, and one-fourth of them was in degree 3 or 4, with manifestations that prevented them from performing ADL and immediate intervention was needed. A study carried out to assess the incidence, mortality rates, and trends of MM in 17 Latin American countries found that structures are fragmented, with a consequent uneven allocation of material and human resources all over this region. In addition, there are few hematologists in Latin America, with estimates of 0.9 hematologists/100,000 inhabitants, whereas the United States has 2.2 professionals/100,000.[16] Hence, staging and scaling of PN symptoms are advanced regarding the disease diagnosis, as found in this work. Another study carried out in the Caribbean and Latin America suggests that delays in pathologic evaluation affect diagnosis and treatment significantly, reducing survival rates.[23]

In view of this, symptoms associated with toxicity are often underestimated by people with cancer due to fear of treatment interruption or dosage reduction with a consequent decrease of its benefit in the control of malignant neoplasia.[12] Moreover, health professionals themselves can underestimate the severity of these symptoms if there is not a reliable measuring method such as Semmes-Weinstein monofilaments, as well as instruments that help in the assessment of PN like the Chemotherapy Induced Neurotoxicity Questionnaire (CINQ), validated in Brazil and made up of questions about the presence of typical symptoms of neurotoxicity in patients.[13]

As for the types of treatment performed for MM, the medical records showed that all patients followed some type of chemotherapy regimen, whether as HSCT pre-conditioning followed by teletherapy, or on its own, and the most used drugs (60%) were bortezomib, dexamethasone, and cy-

clophosphamide. However, in the present sample, there was no statistically significant difference between chemotherapy regimens and PN after treatment. Another study that assessed the efficiency and tolerability of these drugs by individuals with MM stated that PN was observed in some cases and patients with pre-existing PN had their symptoms worsened.[24] Another study which assessed bortezomib-induced PN found an incidence in 55% of participants after treatment was completed.[19]

We can observe that chemotherapy regimens very often include neurotoxic drugs such as bortezomib, cyclophosphamide, and thalidomide. Although an association between the use of these drugs and the development of PN was not found, it is worth noting that 68% of participants used bortezomib, which can induce PN and it is explained by its action mechanism as a consequence of proteasome inhibition, where the back string of the spinal cord is the main target and can lead to a secondary deterioration of the peripheral nerve[19,24], resulting in all the symptoms and risk factors that contribute to the development or maintenance of PN.[6,8,19,24]

Based on these findings, some recommendations can be given to help identify and document PN in MM patients such as: permanent training of professionals who work with this population, creation of evidence-based protocols, assessment of neuropathies by means of validated questionnaires/scales, guidance of patients with regard to the possibility of side effects at the beginning of treatment and measures for vulnerability management to prevent health complications.

A limitation of this study regards its sample being made up of MM individuals cared for in two national institutions, which restricts the possibility of mainstreaming the results. However, this limitation does not invalidate the study and meets satisfactorily its proposals.

Conclusion

Our study showed an increase in the incidence of PN in individuals undergoing treatment of MM, 80% had symptoms of neuropathy before and/or during and/or after treatment with chemotherapy regimens. Predominance was of elderly retired men. The most common chemotherapy regimen was VDC and there was no association between regimens used and PN after treatment. The implications of these observations rest on the need for a permanent assessment of PN in people with MM, in addition to a strict follow-up to this event in the course of treatment and after it, as well as the management of adverse events and alterations related to the disease. There was no association between chemotherapy regimens and peripheral neuropathy after treatment. It is expected that the results obtained help in the organization of a data record about PN in patients with cancer, with the main purpose of establishing targets of intervention, thus making care more efficient and comprehensive.

Collaboration

Moreira MMC, Rodrigues AB, Oliveira PP, Aguiar MIF, Cunha GH, Pinto RMC, Fonseca DF and Mata LRF declare that they contributed to the project conception, data interpretation, relevant critical review of the intellectual content and approval of the final version to be published.

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