ABSTRACT

Objective: To analyze the interventions performed by health professionals with a view to managing chemotherapy-induced febrile neutropenia. Method: Integrative literature review, the sample of 12 primary articles was selected from the following databases: LILACS, SciELO, BVS, PubMed, CINAHL and Web of Science. Results: There was a prevalence of studies, realized by doctors, focused on pharmacological treatment and on the association of methods for greater diagnostic accuracy of febrile neutropenia. A study was found on pharmaceutical management regarding antibiotic dosing efficacy and a study indicating that nurses could contribute to the identification of elderly patients who would benefit from prophylactic use of growth factor. Conclusion: There was a shortage of studies involving the participation of other health professionals, besides the doctors, and a knowledge gap regarding interprofessional practice in the management of interventions specific to their area of specialization, joint interventions and non-pharmacological interventions.

Descriptors: Oncology; Hospital Oncology Service; Chemotherapy-Induced Febrile Neutropenia; Management; Patient Care Team.

RESUMO

Objetivo: Analisar as intervenções realizadas por profissionais de saúde visando ao manejo da neutropenia febril induzida por Quimioterapia. Método: Revisão integrativa da literatura cuja amostra de 12 artigos primários foi selecionada nas bases LILACS, SciELO, BVS, PubMed, CINAHL e Web of Science. Resultados: Constatou-se a prevalência de estudos, desenvolvidos por médicos, centrados no tratamento farmacológico e na associação de métodos para maior precisão diagnóstica da neutropenia febril. Encontrou-se um estudo sobre manejo farmacêutico relativo à eficácia de dosagem de antibióticos e um estudo indicando que os enfermeiros poderiam contribuir para a identificação de pacientes idosos que se beneficiariam com uso profilático de fator de crescimento. Conclusão: Evidenciou-se a escassez de estudos com a participação de outros profissionais de saúde, além dos médicos, e a lacuna de conhecimento quanto à prática interprofissional na condução de intervenções específicas a sua área de competência, intervenções conjuntas e intervenções não farmacológicas.

Descritores: Oncologia; Serviço Hospitalar de Oncologia; Neutropenia Febril Induzida por Quimioterapia; Manejo; Equipe de Assistência ao Paciente.

RESUMEN

Objetivo: Analizar las intervenciones realizadas por profesionales de salud visando el manejo de la neutropenia febril inducida por Quimioterapia. Método: Revisión integradora de la literatura cuya muestra de 12 artículos primarios fue seleccionada en las bases LILACS, SciELO, BVS, PubMed, CINAHL y Web of Science. Resultados: Se constató la prevalencia de estudios, desarrollados por médicos, centrados en el tratamiento farmacológico y en la asociación de métodos para mayor precisión diagnóstica de la neutropenia febril. Se encontró un estudio sobre manejo farmacéutico relativo a la eficacia de dosificación de antibióticos y un estudio indicando que los enfermeros podrían contribuir para la identificación de pacientes de edad avanzada que se beneficiarían...
INTRODUCTION

The treatment of cancer patients is subject to factors which range from diagnostic confirmation of the disease to staging and to individual and psychological characteristics of the patient. There are various therapeutic approaches: hormone therapy, surgical procedures, radiotherapy and chemotherapy (CT)(1). Despite the technological advances, antineoplastic CT continues to be an indispensable therapeutic option. This constitutes a method which uses one or more drugs in order to reach the different cellular populations and in the various phases of the cellular cycle, thereby weakening the development of those cells with disordered growth. The chemotherapies act on tumor cells and also in distinct cells of the body, such as the bone marrow, hair and mucosa of the digestive tract. CT is applied in repetitive cycles, since the normal cell presents a recovery period(2).

The duration of toxic exposure to the drugs depends on the quantity used, the plasma concentration and individual characteristics of each patient. The drugs can lead to toxicities and undesirable effects, such as alopecia, gastrointestinal alterations, myelodepression, fever, and also infectious signs and symptoms. The occurrence of fever in patients undergoing chemotherapeutic treatment represents an oncological emergency, since it is indicative of febrile neutropenia (FN)(3), representing a severe complication with mortality levels that can reach over 50%(4). Axillary temperature measurements greater than 37.8°C, whether single or multiple episodes, already constitutes a warning sign for a picture of FN. Laboratory exams are performed in the presence of fever and diagnosis of FN is confirmed whenever there is a neutrophil count less than 500/mm³, or a reduction to less than 500 neutrophils/mm³ within the following 48 hours(5).

Individuals with FN can be classified as low-risk, intermediate-risk and high-risk neutropenic patients. The risk score is determined using the MASCC (Multinational Association for Supportive Care of Cancer) risk index, which allocates points according to the importance of each variable: asymptomatic patient; patient presenting mild, moderate or severe symptoms; no hypotension; no chronic obstructive pulmonary disease; solid tumor with no previous fungal infection; no dehydration; outpatient status at onset of fever; and age under 60 years. The MASCC risk index has a maximum score of 26 points and classifies the patients into low-risk (≥ 21 points) or high-risk (< 21 points)(5). It is widely used and considered to be simple, while presenting good sensitivity and a high positive value.

It should be noted that patients with hematologic neoplasia reach an initial score, regardless of any other conditions, up to a maximum of 22 points; implying a high rate of hospitalization that is not always necessary and incurs high costs to the health system(7). Patients considered to be high-risk should receive broad-spectrum intravenous antibiotic therapy (ABT) and indicated for hospitalization; Patients with low-risk and intermediate-risk of complications may be considered candidates for ABT orally or intravenously and without hospitalization(8).

The focus of infection is not always clearly defined in neutropenic patients admitted to the health services, even with clinical anamnesis, since fever may be the only sign of infection. Thus, empiric treatment with broad-spectrum antibiotics is initiated early so that future complications are avoided(9).

Management of FN varies according to each health institution, such that establishing care guidelines based on the MASCC risk index would allow patients to benefit from complete treatment, reduce the variation of conduct in care provided, optimize decision making and thereby, improve care quality and treatment results(10).

Considering that FN is a complication induced by chemotherapy treatment, which can incur high mortality rates and faced with increasing hospital costs, it requires proper management to ensure the best results for both patients and the health institution. Consequently the present study was conducted with the objective of analyzing the interventions performed by health professionals for management of CT induced FN in adult patients.

METHOD

An integrative review of the literature was performed since this is considered a unique tool in the field of health, by enabling the synthesis of available evidence on a given theme and directs clinical practice based on scientific knowledge(11). The guiding research question was: “What are the interventions developed by health professionals, as reported in the literature, for the management of CT induced FN in adult oncology patients?”

The integrative review was organized with the PICO search strategy, which is an acronym for Patient or Problem, Intervention, Control or comparison and Outcome; the abbreviations in this study were defined as: “P” - adult oncology patients submitted to CT; “I” - interventions performed by health professionals; “C” - not applicable as no intervention was established for comparison; and “O” - FN management. The research was undertaken in the following steps: establishment of the hypothesis and objective; establishment of inclusion and exclusion criteria for articles (sample selection); definition of the information to be extracted from selected articles; analysis of results; presentation and discussion of results; and finally, presentation of the review(12).
In order to select the articles, databases were used to broaden the scope of the search: LILACS (Latin American and Caribbean Literature in Health Sciences), SciELO (Scientific Electronic Library Online), BVS (Virtual Library of Health), PubMed, CINAHL (The Cumulative Index to Nursing and Allied Health Literature) and Web of Science.

The inclusion criteria were: primary articles published in Portuguese, English or Spanish, with their entire texts available in the selected databases, published between 2010 and 2015; articles whose methodology demonstrated interventions related to the practices of health team professionals (either in conjunction or individually) for the management of CT-induced FN in adult patients.

As recommended by Lopes, Galvão, due to the specific characteristics of accessing each of the selected databases, the strategies used to locate the articles were adapted according to the research questions and the inclusion criteria to maintain consistency in the search for articles and avoid possible biases. From this perspective, the keywords used were: febrile neutropenia/oncology, febrile neutropenia/cancer, fever/ chemotherapy neutropenia, febrile neutropenia/chemotherapy-induced, febrile/classification neutropenia, febrile neutropenia/complications, febrile/therapy neutropenia, febrile neutropenia/treatment, febrile neutropenia/management, febrile neutropenia/mucositis, febrile neutropenia/hematology, fever/nursing neutropenia, febrile/dental neutropenia, febrile/ pharmacy neutropenia, febrile neutropenia/social service, febrile neutropenia/nutrition, febrile neutropenia/febrile neutropenia and medicine/medical.

The online search found 2,892 articles; after applying the inclusion criteria, the final sample for this integrative review comprised 12 articles, as shown in Figure 1.

Data collection of primary articles included in the integrative review was made possible through an instrument detailing: identification of the original article (title, periodical, authors, specialization of authors, year of publication); objective(s); methodological characteristics of the study (type, sample, specialization of the professionals involved in FN management); intervention for FN management; and main findings, conclusions and identification of limitations and/or biases. For the analysis and synthesis of these articles, we used synoptic tables containing: title, author/year and professional category; interventions realized; results; and recommendations/conclusions.

**RESULTS**

This integrative review located a sample of 12 articles which met the inclusion criteria and are presented in Chart 1. All of the studies analyzed were performed in hospital institutions, of which 10 by doctors, one by a pharmacist and one by nurses. They were published in the following journals: Support Care Cancer (3), Clinical Journal of Oncology Nursing (1), Journal of Clinical Oncology (1), BMC Pharmacology and Toxicology (1), Farmacia Hospitalaria (1), European Journal of Cancer Care (1), Supportive Care in Cancer (1), BMC Infectious Diseases (1), Journal of Oncology Practice (1) and International Journal of Infectious Diseases (1).

**Chart 1** – Characterization of the 12 primary articles included in the integrative review, according to title, author, year and professional category, São Paulo, Brazil, 2016

<table>
<thead>
<tr>
<th>Title</th>
<th>Author/year</th>
<th>Professional category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing neutropenia in older patients with cancer receiving chemotherapy in a community setting</td>
<td>Flores QI, Ershler W; 2010</td>
<td>Nurse</td>
</tr>
<tr>
<td>Safety of Early Discharge for Low-Risk Patients With Febrile Neutropenia: A Multicenter Randomized Controlled Trial</td>
<td>Talcott JA, et al.; 2010</td>
<td>Doctor</td>
</tr>
<tr>
<td>Pharmacokinetics of piperacillin/tazobactam in cancer patients with hematological malignancies and febrile neutropenia after chemotherapy</td>
<td>Álvarez JC, et al.; 2013</td>
<td>Doctor</td>
</tr>
</tbody>
</table>
In relation to the type of study, three were “retrospective cohort”; two “randomized controlled”; two “multicenter randomized prospective”; two “prospective observational”; one “prospective descriptive”; one “retrospective observational”; and one “prospective cohort”. A summary of the contents (Intervention, Results and Recommendations/Conclusion) of each article is presented in Chart 2.

Regarding the interventions for management of CT-induced FN, there was a prevalence of studies focused on pharmacological treatment (use of empiric ABT in hospital and outpatient settings, adherence to an antimicrobial management protocol and use of prophylactic or non-prophylactic growth factor)\(^{[14-15,18-24]}\) and improvement in the diagnostics (association of biomarkers with the MASCC risk index)\(^{[17]}\). Only one study\(^{[16]}\) investigated pharmaceutical management in relation to the efficacy of antibiotic dosage and a study which implied that nurses could contribute to the identification of elderly patients who would benefit from prophylactic use of growth factor in order to reduce the occurrence of FN\(^{[13]}\).

**Chart 2** — Presentation of the synthesis of interventions, results and recommendations/conclusions for each of the 12 primary articles included in the integrative review, São Paulo, Brazil, 2016

<table>
<thead>
<tr>
<th>Title</th>
<th>Author/year</th>
<th>Professional category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Análisis descriptivo de los motivos que originan visitas a urgencias en pacientes oncológicos: toxicidad postquimioterapia(^{[16]})</td>
<td>Bravo SB, et al.; 2013</td>
<td>Pharmacist</td>
</tr>
<tr>
<td>C-reactive protein and the MASCC risk index identify high-risk patients with febrile neutropenia and hematologic neoplasms(^{[17]})</td>
<td>Juan F, Lombana M, Pino LE, Arango M; 2013</td>
<td>Doctor</td>
</tr>
<tr>
<td>Adding procalcitonin to the MASCC risk-index score could improve risk stratification of patients with febrile neutropenia(^{[18]})</td>
<td>Ahn S, Lee YS, Lim KS, Lee JL; 2013</td>
<td>Doctor</td>
</tr>
<tr>
<td>Feasibility and safety of a reduced duration of therapy of colony-stimulating factor in a dose-dense regimen(^{[20]})</td>
<td>Puccini LRB, et al.; 2014</td>
<td>Doctor</td>
</tr>
<tr>
<td>Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study(^{[21]})</td>
<td>Rosa RG, Goldani LZ, Santos RP; 2014</td>
<td>Doctor</td>
</tr>
<tr>
<td>Incidence, treatment, and consequences of chemotherapy-induced febrile neutropenia in the inpatient and outpatient settings(^{[22]})</td>
<td>Weycker D, Barron R, Kartashov A, Adicionar J, Lyman GH; 2014</td>
<td>Doctor</td>
</tr>
<tr>
<td>Randomized controlled trial comparing ciprofloxacin and cefepime in febrile neutropenic patients with hematological malignancies(^{[23]})</td>
<td>Yasuda T, et al.; 2014</td>
<td>Doctor</td>
</tr>
<tr>
<td>Value of lipopolysaccharide binding protein as diagnostic marker of infection in adult cancer patients with febrile neutropenia: comparison with C-reactive protein, procalcitonin, and interleukin(^{[24]})</td>
<td>Garcia GRL, et al.; 2015</td>
<td>Doctor</td>
</tr>
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</table>

Note: MASCC - Multinational Association for Supportive Care of Cancer.
**DISCUSSION**

The proven relevance of the use of growth factor as a prophylaxis in elderly patients with breast cancer and lymphoma is well-known since they are more likely to develop FN episodes (neutrophils \( \geq 1000 \)) \(^{17}\). This prophylactic intervention, performed after CT, decreases the occurrence of FN episodes. According to the clinical practice of the authors, the use of growth factors as drug intervention is essential to avoid the occurrence of FN, associated with performing a complete blood count and monitoring the results.

Regarding the efficacy of antimicrobial use, a study demonstrated the benefits of using piperacillin/tazobactam in treating FN and prevention of complications\(^{18}\). In another study, adherence to an antimicrobial management protocol enabled a reduction in the mortality rate\(^{19}\). When comparing efficacy...
between cefepime and ciprofloxacin, a study recommended that cefepime be used as the initial standard treatment of choice for FN and ciprofloxacin as an empiric and prophylactic treatment. Thus, the significant efficacy of cefepime treatment on day 7 of CT has been demonstrated, resulting in a better response in neutrophil counts of high-risk FN patients\(^{(20)}\). It should be emphasized that the rational use of antimicrobial therapy has a favorable effect on FN management, while reducing hospital costs and lowering mortality rates. In the hospital context in which the investigators of the present research work, there are protocols established for each degree of FN, and empirical ABT is administered until confirmation of culture results and, subsequently, ABT according to the sensitivity of the bacterium.

Pharmacological prophylactic treatment in an outpatient setting reduces the mortality rate and prolonged hospitalization, thereby reducing hospital costs\(^{(23)}\). Early hospital discharge for patients classified as low risk, combined with adequate ABT and ambulatory follow-up and/or supervision, attenuates the occurrence of complications and reduces both hospital costs and also outpatient treatment costs, while improving the patient’s quality of life\(^{(14)}\). In the clinical practice of the authors, those classified as low-risk neutropenic patients are usually treated with ambulatory ABT and a weekly follow-up.

Studies that associated the identification of biomarkers (C-reactive, PCT, interleukin)\(^{(17,19,24)}\) with the results of the MASCC risk index obtained higher accuracy in the score and in identification of the severity of FN and its complications (bacteremia and septic shock). Based on their clinical practice the authors have noted that even though identification of CT-induced FN using the MASCC risk index is recommended by the institution’s current guidelines, it is still not fully applied -which constitutes a challenge to be faced.

Despite the methodological option to expand the keywords, the present integrative review has demonstrated a lack of studies addressing non-pharmacological interventions for the management of CT-induced FN and also a lack of studies related to the practice of some health professionals and the team.

These results have drawn the authors’ attention, since in the hospital in which they are employed, they observe the daily work of other professionals in the health team (such as nutritionists, social workers, psychologists and nurses) developing non-pharmacological interventions that are integrated with their Interprofessional Practice (IPP).

The nutritionist proposing a specific diet for neutropenic patients, in order not to expose them to foods that could lead to infection due to their immunodepression.

The social worker analyzing the conditions that prevent patients from going to the hospital to receive treatment and/or prophylaxis with growth factor (Filgrastim); indicating that the patient should use the medication at home, in situations such as bedridden, impaired mobility, residing in another municipality or state and vulnerability; including making health facilities available at the place of residence of these patients in cases where transport is not available for them to receive the prescribed antimicrobial and G-CSF on a daily basis.

The nurse responsible for the guidelines and care intended to prevent the occurrence of infection, as well as supervising and monitoring the patient’s myelodepression in the NADIR period, time elapsed between the application of the drug and the occurrence of the lowest hematological count\(^{(25)}\), and when there could be a drop in the neutrophils, checking the laboratory tests and administering the prescribed treatment.

The psychologist participating in providing emotional assistance to help patients face the disease, as well as to encourage adherence to the proposed treatment and avoiding interruptions due to absenteeism.

The dentist contributes both to the prevention and treatment of mucositis, using laser therapy, since an open lesion in the buccal region leads to the appearance of infection in patients submitted to CT.

Therefore, in view of the present results and reality of the disease, it is reiterated that the occurrence of FN, since it constitutes an important risk for the well-being and survival of patients under chemotherapy treatment, requires the presence of highly qualified health professionals and knowledge based on scientific evidence. From this perspective, it is necessary to develop studies that give visibility to the IPP to ensure successful management of CT-induced FN.

It is imperative to emphasize IPP in different contexts of health services, since it allows problematization and, consequently, a possible displacement of the acknowledged fragmentation to the articulation and integration of health actions; it also tends to increase the resolutivity of services and the quality of health care, to increase and improve communication between professionals and to give recognition to the specific contributions of each area and its overlapping borders\(^{(26)}\).

**Study limitations**

The low number of studies found in the literature is considered to be a limitation; it is recommended that future studies use a broader database.

**Contribution to the area of nursing health or public policy**

The present study synthesized the main results and recommendations of research on the interventions performed by health professionals for management of CT-induced FN in adult patients. By sharing the experience of a public hospital institution, specialized in teaching, research and humanized treatment of cancer patients, especially in the conduct of non-pharmacological interventions, it constitutes an advance in the verticalization of knowledge on the subject.

**CONCLUSION**

In this integrative review, 12 primary studies were selected and analyzed the objectives of which were to investigate interventions for the management of CT-induced FN. Most were performed by doctors with an emphasis on pharmacological treatment with antimicrobials and/or growth factors and associations of methods for greater diagnostic accuracy of FN.

The scarcity of studies with the participation of other health professionals and lack of knowledge regarding IPP was evident, especially in the conduct of interventions specific to their area of competence, joint interventions and non-pharmacological interventions.
The IPP, aiming at FN management, with the use of prophylactic drugs, accurate diagnosis, monitoring and treatment (pharmacological and non-pharmacological), contributes to the achievement of effective results, such as improvement in quality of life and adherence of patients to the treatment regimen, reduction in hospitalization rates, lower mortality rates and, consequently, lower tangible and intangible costs. Thus, the relevance and necessity is reiterated for the development of studies to confer visibility to Interprofessional Practice by broadening and deepening the scientific knowledge related to this question.

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