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Management of chemotherapy-induced febrile neutropenia and use of granulocyte colony-stimulating factor in patients with soft tissue or bone sarcoma

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Abstract

Introduction: Febrile neutropenia, an oncological complication related to myelosuppressive chemotherapy, can lead to unplanned hospitalization, morbidity, mortality, and changes in the oncological therapeutic plan. The present study aimed (1) to determine the prevalence of chemotherapy-induced febrile neutropenia requiring hospitalization and the use of granulocyte colony-stimulating factor and (2) to evaluate its consequences for the oncological treatment of patients with soft tissue or bone sarcomas.

Methods: This is a cross-sectional and retrospective study (January 2018 to December 2019) carried out in a reference oncology hospital in the Brazilian public health system. Inpatients diagnosed with chemotherapy-induced febrile neutropenia, older than the age of 18 years, and treated with granulocyte colony-stimulating factor were included in the study.

Results: Twenty-nine chemotherapy-induced febrile neutropenia events were identified, involving 25 patients. Among the febrile neutropenia events, 90% were grade 4, and 59% occurred during palliative chemotherapy. Among patients with febrile neutropenia, 31% had arterial hypertension or/and diabetes mellitus comorbidities, 34% had infectious skin sites, such as compression ulcers and tumor wounds, and 31% had infections with defined etiologic agents. Treatment of hospitalized patients was performed with cefepime in combinations or alone (97%) and filgrastim. The outcomes related to chemotherapy-induced febrile neutropenia were chemotherapy dose reduction (31%), chemotherapy cycle delays (21%), chemotherapy treatment suspension (17%), deaths (7%), and other associated complications (10%). Granulocyte colony-stimulating factor prophylaxis was prescribed in 72.41% of febrile neutropenia events. The frequency of febrile neutropenia concerning total chemotherapy cycles was 2.15%.

Conclusion: Even with granulocyte colony-stimulating factor prophylaxis, an overall prevalence of 2.15% of febrile neutropenia associated with hospitalization was observed, causing negative outcomes in chemotherapy treatment of patients.

Keywords

Febrile neutropenia, sarcomas, granulocyte colony-stimulating factor, filgrastim, chemotherapy-induced febrile neutropenia

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Introduction

Sarcomas are rare malignant neoplasms with mesenchymal origin. They are classified into soft tissue sarcomas or bone sarcomas, which correspond to more than 70 types of malignancies with heterogeneous histological and clinical characteristics. Sarcomas account for 1% of tumors diagnosed in young adults. Undifferentiated pleomorphic sarcomas, liposarcoma, leiomyosarcoma, myxofibrosarcoma, and synovial sarcoma are the most frequent in the adult population. Soft tissue sarcomas have a worldwide incidence of 1.8 to 5.0 per 100,000 person-years. Bone sarcomas are even rarer and account for 0.2% of cancer cases.[1–3]

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The treatment of sarcomas includes different approaches, such as radiotherapy and chemotherapy. Adjuvant, neoadjuvant, or palliative chemotherapy can trigger several adverse events. Among the hematological toxicities associated with antineoplastic therapy, we can highlight febrile neutropenia (FN).[4]

FN is an oncological emergency resulting from myelotoxic chemotherapy treatment and generates negative consequences for the patient's therapeutic plan, requiring rapid and adequate management. According to the American Society of Clinical Oncology (ASCO) definition, neutropenia is characterized by a neutrophil count below 1000 neutrophils/μL, and it can be classified as severe (< 500 neutrophils/μL) or profound (< 100 neutrophils/μL). If neutropenia is associated with a fever greater than 38.3°C or 38.0°C sustained for more than 1 h, it can be classified as NF.[5]

FN has an incidence of 8–54% in patients with bone or connective tissue cancer who receive treatment with myelotoxic chemotherapy drugs such as doxorubicin, cisplatin, cyclophosphamide, ifosfamide, and etoposide. The period of hospitalization associated with FN can vary from 5 to 10 days, leading to unfavorable clinical outcomes, increased morbidity, mortality, and hospital costs.[6–9]

The use of an instrument that stratifies patients according to the risk of developing complications resulting from FN, such as the Multinational Association of Supportive Care in Cancer (MASCC) is important to define prevention measures based on risk factors (comorbidities, age, type of tumor, staging, hypotension, and performance status).[8,10]

FN patients have a 50% more chance of infections, of which 20% may progress to bacteremia. Generally, the sites of infections reported are respiratory, gastrointestinal, and cutaneous. Regions with an implanted catheter should also be evaluated as potential areas of infection in these patients. Commonly, the microbiological findings are Gram-negative bacteria, but infections with Gram-positive bacteria or fungi can also occur.[11,12]

According to guidelines published by ASCO, European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN), empiric broad-spectrum antibiotic therapy needs to be started within 1 h after the presentation of signs and symptoms of conditions associated with FN. Delayed initiation of antibiotic therapy is often associated with increased mortality risk, especially in Gram-negative bacteria infections.[12,13]

Contrary to the well-established recommendation for antibiotic therapy, the use of granulocyte colony-stimulating factors (G-CSFs) for the treatment of FN is controversial. G-CSF use is advised in severe neutropenia (grades 3 or 4), in the presence of risk factors, and, in prophylactic protocols, as summarized in Table 1.[12,14–16] Some studies show that the use of antibiotic therapy associated with G-CSF reduces the length of hospital stay; however, it does not reduce the mortality associated with chemotherapy-induced FN (CIFN).[11]

Prophylactic therapy with G-CSF, such as filgrastim, is associated with reduced incidence of FN and infections-related complications. On the other hand, filgrastim is related to musculoskeletal pain, fever, leukocytosis, and anaphylactic reactions. Therefore, prophylactic use is recommended for patients receiving chemotherapy regimens at increased risk of developing FN. According to the EORTC (European Organization for Research and Treatment of Cancer) and the NCCN, protocols such as ifosfamide/doxorubicin, isolated doxorubicin and doxorubicin/ifosfamide/ mesna/dacarbazine, used for the treatment of soft tissue sarcomas, are 20% more likely to cause FN. Additionally, in the treatment of osteosarcomas, the most myelotoxic chemotherapy regimens are vincristine/doxorubicin/cyclophosphamide, Vincristine/Dactinomycin/cyclophosphamide, and cisplatin/doxorubicin.[7,14,15]

Considering the high morbidity and mortality associated with FN and its impact on cancer treatment, the present study aimed to analyze the prevalence and management of CIFN and the use of G-CSF in patients diagnosed with soft tissue or bone sarcoma, hospitalized in a referral oncology hospital, belonging to the Public Health System. Patients' profiles, adherence to the international guideline's recommendations, therapeutic response to G-CSF and antibiotic therapy, and the FN impact on cancer treatment were evaluated.

Methods

This is a cross-sectional, retrospective (January 2018 to December 2019), and single-center study approved by the local research ethics committee (Ethics committee of the Brazilian National Cancer Institute, INCA, Brazil, Rio de Janeiro, CAAE 46834621.3.0000.5274).

The study included in-patients with a diagnosis of bone or soft tissue sarcomas, undergoing chemotherapy, older than 18 years, with at least one prescription of filgrastim during hospitalization, and FN reported in electronic or physical medical records. Patients with missing data were considered ineligible.

FN episodes were identified by the use of G-CSF, absolute neutrophil counts (< 1000 cells/μL), and a reported fever (>38.3°C or 38.0°C sustained for more than 1 h). The intensity of neutropenia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[17]

G-CSF prophylaxis was verified by the outpatient dispensation of filgrastim, associated with the infusion period of the chemotherapy protocol. The prevalence of CIFN, with consequent hospital admission and use of G-CSF, was calculated based on the total number of chemotherapy cycles performed to treat patients with bone or soft tissue sarcomas over the two years analyzed.

The variables analyzed in this work were: demographic (sex and age group), clinical (type of cancer, staging, chemotherapy protocol used, and hospitalization time), laboratory (C-reactive protein, creatinine, urea, blood culture, urine culture, oropharyngeal and anal swab), and risk factors (previous exposure to chemotherapy, neutropenia grade, infectious

sites, previous colonization, and comorbidities), like recommended by the ASCO.

The outcomes analyzed were compliance with international guidelines (ASCO, NCCN, and ESMO) in the management of FN and its impact on the patient's chemotherapy regimen.

The pharmacological treatment of FN in hospitalized patients was verified through the analysis of electronic prescriptions. In addition, the patients' chemotherapy regimens were obtained from the institutional database of the chemotherapy dilution center. The therapeutic response to FN treatment was evidenced by the length of stay, blood neutrophil counts, and the presence of associated complications, including death. The FN impact on the patient's therapeutic plan was verified based on the occurrence of delay, suspension, or dose reduction in the anticancer treatment.

The data were analyzed using descriptive statistics. Qualitative variables were expressed as absolute frequency and/or percentage, while quantitative variables were expressed as mean, median, and SD.

Results

In the study period, 29 FN events required hospitalization and treatment with G-CSF. The events involved 25 patients with a mean age of 41 years and a median of 34 years (SD ± 19.99), ranging from 18 to 85 years (Table 2).

Among the patients who developed FN (n = 25) associated with chemotherapy, 40% (n = 10) were aged between 18 and 30 years, 56% (n = 14) were male and 28% (n = 7) had a diagnosis of osteosarcoma. About 59% (n = 17) of FN events occurred during palliative chemotherapy and 21% (n = 7) during treatment with the cisplatin/doxorubicin protocol (Table 2).

Two patients (8%) received two different chemotherapy protocols during the study period and developed FN in both (1-doxorubicin/cisplatin, and ifosfamide and 2-vincristine/doxorubicin/cyclophosphamide, and ifosfamide).

Regarding cancer staging, 12 patients had a metastatic focus (41%), and one developed FN before and after being diagnosed with metastasis (Table 2).

FN hospitalization events occurred between the first and second cycles of chemotherapy in 65% of cases (n = 19), with 17% (n = 5) of events between cycles 3 and 4, and 14% (n = 4) between cycles 5 and 6.

Considering the risk factors reported in international guidelines, among the 29 FN events observed in the study, 37.93% (n = 11) occurred in patients with an implanted catheter. One patient had episodes of FN before and after catheter implantation. About skin injuries, as possible foci of infection, regardless of the region, 34.48% (n = 10) of the events occurred in the presence of a tumor wound, compression ulcer, abscess, or cellulitis. The search for an etiologic agent associated with FN was based on laboratory findings from blood cultures, urine cultures, and screening swabs at the time of admission. Ten etiologic agents were identified related to 9 (36.00%) FN events. One patient had a positive nasal swab for *Staphylococcus aureus* and positive urine culture for *Pseudomonas aeruginosa*. In four events (13.79%), there was a report of contact precautions due to a previous history of colonization by resistant microorganisms (Table 3).

Among the FN episodes, 68.86% (n = 20) corresponded to patients without comorbidities. On the other hand, two patients had multiple comorbidities (hypertension + lupus or hypertension + diabetes mellitus). About previous exposures, 55.17% (n = 13) of the events occurred in patients with previous radiotherapy and/or chemotherapy treatment, or with previous cases of FN reported in the medical records (Table 3).

Table 1. Risk factors and recommendations for managing febrile neutropenia (FN) in outpatients or patients undergoing chemotherapy.

Risk factors	• Oncological: Staging of cancer, low-performance status, tumor type (solid or hematological). • Therapeutic: Treatment cycle, previous exposures (chemotherapy or radiotherapy). • Comorbidities: Cardiovascular disease, liver or kidney dysfunction, multiple comorbidities, HIV. • Clinical: Age over 65 years, previous infections, mucositis, open wounds, persistent neutropenia, previous FN event, absence of prophylaxis (antibiotic and G-CSF).
Prophylaxis	• High-risk chemotherapy protocols > 20%[a]/patients with MASCC[b] less than 21 points: Prophylactic G-CSF is recommended. • Low-risk chemotherapy protocols < 10%[a] patients with MASCC greater than 21 points: Prophylactic G-CSF is not recommended.
Management	• Outpatient (low-risk patients, MASCC > 21 points): Clinical analysis[c], oral antibiotic therapy. • Inpatient (high-risk patients, MASCC < 21 points): Intravenous broad-spectrum antibiotic therapy.

[a]Classification according to EROCT.

[b]The Multinational Association for Supportive Care in Cancer (MASCC) score, in which the patient is scored according to the criteria such as symptomatology, age, tumor type, lung disease, hypotension, and performance status.

[c]Hemodynamically stable patients without acute leukemia, pneumonia, catheter implanted, soft tissue infection, solid tumor, and neutropenia for less than 7 days.

G-CSF: granulocyte colony-stimulating factors; HIV: human immunodeficiency virus.[12,15,16]

Table 2. Demographic and clinical profile of patients who developed chemotherapy-induced FN (CIFN).

Demographic profile	N	% (n = 25 patients)
Age (Median = 34 years, SD ± 19.99)		
18–30 years old	10	40.00
30–60 years old	8	32.00
More than 60 years old	7	28.00
Gender		
Female	11	44.00
Male	14	56.00
Clinical profile	N	% (n = 25 patients)
Types of cancer		
Osteosarcoma	7	28.00
Primitive neuroectodermal tumor (PNET)	3	12.00
Ewing sarcoma	3	12.00
Endometrial carcinosarcoma	2	8.00
Pleomorphic sarcoma	2	8.00
Angiosarcoma	1	4.00
Chondrosarcoma	1	4.00
Desmoplastic small round cell tumor	1	4.00
Rhabdomyosarcoma	1	4.00
Kaposi sarcoma	1	4.00
Retroperitoneal sarcoma	1	4.00
Fibromyxoid sarcoma	1	4.00
Peripheral nerve sarcoma	1	4.00
Chemotherapy	N	% (n = 29 events)
Purpose		
Palliative	17	58.62
Neoadjuvant	8	27.58
Adjuvant	4	13.79
Chemotherapy regimens		
Cisplatin/Doxorubicin[a]	6	20.69
Doxorubicin[a]	5	17.24
Ifosfamide/Etoposide	5	17.24
Vincristine/Doxorubicin/ cyclophosphamide[a]	5	17.24
Ifosfamide	3	10.34
Carboplatin/Paclitaxel	2	6.90
Ifosfamide/Doxorubicin[a]	1	3.45
Vinblastine D1/D8	1	3.45
Vincristine/Dactinomycin/ cyclophosphamide[a]	1	3.45
Presence of metastasis		
Yes	12	41.39
No	17	58.62

[a]Protocols are considered high risk for developing FN according to the recommendations published by NCCN, 2021.

FN was ranked according to CTCAE 5.0, revealing that 89.65% (n = 26) of events were grade 4 (severe neutropenia) (Table 3).

The mean length of hospital stay for FN events was 9.1 days, with a minimum of 3 days and a maximum of 57 days. Events with a hospital stay longer than 20 days (n = 2, 6.89%) were associated with deaths, one due to renal failure and the other due to sepsis (Table 5).

All patients admitted for FN had antibiotic therapy prescribed within the first 24 h of hospitalization. The protocol cefepime 2 g every 8 h was used in 68.96% (n = 20) of the cases. In 14 events (48.27%) antibiotic therapy was completed during hospitalization and, in the remaining cases, in outpatient treatment (Table 4).

The patients were treated with G-CSF to promote an increase in the number of neutrophils. The mean period of filgrastim consumption by hospitalized patients was 3.6 days with a minimum of 2 and a maximum of 6 days. The mean neutrophil recovery time (>500 neutrophils/μL) was 2.3 days, ranging from 1 to 7 days (Table 4).

The FN episodes caused alterations in the patient's oncological treatment plan in 82.75% (n = 24) of the cases. The negative outcomes associated with this severe hematologic adverse reaction were delay (20.68%), dose change (31.03%), protocol change (20.68%), and discontinuation (17.24%) of chemotherapy treatment (Table 5). In the same FN event, several impacts on cancer treatment were observed, such as dose reduction, cycle delay, and finally change of chemotherapy protocol. Regarding protocol changes, five patients migrated to another protocol, and one had only one chemotherapy agent excluded.

As previously reported, two cases of FN evolved to patient death due to complications such as renal failure and sepsis. In addition, both patients had associated comorbidities, skin infections, and other clinical conditions besides the FN at the time of hospital admission.

Considering the myelotoxic potential of several chemotherapy protocols used in the treatment of sarcomas and the conflicting data in the scientific literature regarding the recommendation of G-CSF prophylaxis, the prophylactic consumption of filgrastim between patients with FN events was evaluated.

Among the twenty-nine events of hospitalization for CIFN, 21 (72.41%) reported prophylaxis with filgrastim 300 mcg/day, subcutaneously, for five days, starting 24 h after the chemotherapy infusion. Of the 8 (27.58%) events of FN without previous G-CSF prophylaxis, 5 (17.24%) were associated with doxorubicin, two (6.89%) with the carboplatin/paclitaxel, and 2 (3.44%) with the vinblastine protocols.

The protocols vinblastine, and carboplatin/paclitaxel, when compared to their overall rate of administration in patients with bone and soft tissue sarcomas, showed a higher percentage of FN occurrence, with 100%, and 28.57%, respectively. However, the small number of cycles of these protocols indicates that they are not included in the institutional standard of care and require future investigations to obtain more robust results (Table 6).

The doxorubicin protocol, classified as high risk for FN, was the most prescribed and had a low prevalence of FN (1.88%). However, all episodes observed (n = 5) occurred in cycles without G-CSF prophylaxis.

Table 3. Risk factors and comorbidities associated with febrile neutropenia (FN).

Risk factors	N	% (n = 29 events)
Implanted catheter	11	37.93
Skin infection		
No skin infection reported	19	65.51
Skin infection reported	10	34.48
Tumor wound	7	24.13
Compression ulcer	1	3.44
Abscess	1	3.44
Cellulitis	1	3.44
Research of microbiological agents		
Negative culture	20	68.96
Positive culture	9	31.03
Identified microorganisms	10*	-
Pseudomonas aeruginosa	1	3.44
Escherichia coli	1	3.44
Pandoraea spp	1	3.44
Klebsiella pneumoniae	1	3.44
Enterobacter cloacae complex	1	3.44
Streptococcus parasanguinis	1	3.44
Staphylococcus hominis	2	6.89
Staphylococcus aureus	1	3.44
Methicillin-resistant Staphylococcus aureus	1	3.44
Comorbidities		
No comorbidities	20	68.96
Diabetes mellitus 2	1	3.44
Arterial hypertension	5	17.24
Human immunodeficiency virus	1	3.44
Multiples comorbidities	2	6.89
Laboratory parameters		
Renal function		
Creatinine $\geq$ 1.3 mg/dL[a]	4	13.79
Urea $\geq$ 50 mg/dL[b]	1	3.44
C-reactive protein[c]		
0.5–25 mg/dL	22	75.86
25–60 mg/dL	4	13.79
Not reported	3	10.34
Associated conditions at the time of hospital admission		
Mucositis	3	10.34
Gastrointestinal symptoms [A]	7	24.13
Respiratory symptoms [B]	7	24.13
Fever [C]	25	86.20
Grade of neutropenia (CTCAE 5.0)		
Grade 3 (500–1000 neutrophils/μL)	3	10.34
Grade 4 (<500 neutrophils/μL)	26	89.65
Previous exposure to chemotherapy		
No	16	55.17
Yes	13	44.82
Previous exposure to radiotherapy	7	24.13
Previous history of FN	5	17.24

*One patient had a positive nasal swab for *Staphylococcus aureus* and positive urine culture for *Pseudomonas aeruginosa*.
[a]Creatinine reference values: 0.3 to 1.3 mg/dL.
[b]Reference values for urea: 10 to 50 mg/dL.
[c]Reference value for C-reactive protein: $\leq$ 0.5 mg/dL.
[A]Gastrointestinal symptoms comprised diarrhea, emesis, nausea, and abdominal pain.
[B]Respiratory symptoms comprised cough, sinusitis, or pneumonia as reported in the medical records.
[C]Fever greater than 38.3°C on hospital admission or after chemotherapy infusion (patient's verbal report).
CTCAE: Common Terminology Criteria for Adverse Events.

Table 4. Antibiotic and granulocyte colony-stimulating factor (G-CSF) therapy in the management of febrile neutropenia (FN).

Management of the FN	N	% (n = 29 events)
Initial intravenous antibiotic therapy (first 24 h)		
Cefepime 2 g 8/8 h	20	68.96
Cefepime 2 g 12/12 h	1	3.44
Cefepime 2 g + clarithromycin 1 g	1	3.44
Cefepime 2 g + vancomycin (1 g/1.2 g/ 1.5 g)	6	20.68
Meropenem 2 g + vancomycin 750 mg	1	3.44
Hospital discharge and outpatient antibiotic therapy segment		
Yes	14	48.27
No	15	51.72
Outpatient antibiotic therapy		
Amoxicillin + clavulanate (500 mg/125 mg) + ciprofloxacin (500 mg)	5	17.24
Amoxicillin + clavulanate (500 mg + 125 mg)	4	13.79
Ciprofloxacin (500 mg)	2	6.89
Others	3	10.34
Time of G-CSF therapy (filgrastim, 300 mcg/day, SC)		
1–2 days	7	24.13
3–4 days	12	41.37
5–6 days	7	24.13
7–10 days	3	10.34
Neutrophil recovery time (> 500 neutrophils/μL)		
1–2 days	18	62.06
3–4 days	8	27.58
5–6 days	2	6.89
7 days	1	3.44

SC: subcutaneous administration.

Table 5. Impact of febrile neutropenia (FN) in the oncological treatment plan and clinical outcomes.

Clinical outcomes	N	% (n = 29 events)
Period of hospitalization		
1–4 days	7	24.13
5–9 days	16	55.17
10–15 days	4	13.79
More than 20 days	2	6.89
Clinical complications		
Renal failure	1	3.44
Sepsis	1	3.44
Hypotension	1	3.44
Impact on the oncological therapeutic plan		
Yes	24	82.75
No	5	17.24
Outcomes on the oncological therapeutic plan		% (n = 29 events)
Chemotherapy cycles delay	6	20.68
Up to 20 days	5	17.24
More than 20 days	1	3.44
Chemotherapy dose reduction	9	31.03
10–15%	2	6.89
20–25%	7	24.13
Chemotherapy regimen alteration	6	20.68
Chemotherapy suspension	5	17.24
Death	2	6.89

The total number of chemotherapy cycles over the 2 years evaluated in the study was determined to establish the prevalence of CIFN. Of the 1346 global chemotherapy cycles performed, 2.15% (29 cases) resulted in FN events, which require hospitalization and the use of G-CSF (Table 6).

Discussion

This retrospective work, conducted in a national reference cancer center, demonstrated a prevalence of 2.15% of CIFN, requiring hospitalization and G-CSF use, in bone or soft tissue sarcomas patients. Clinical and epidemiological characteristics of the patients indicated a population with a high risk to develop FN. Altogether, the data revealed that the prophylactic and therapeutic approaches adopted were compatible with the recommendations of international guidelines. The use of G-CSF to prevent and/or recover FN events was observed in high-risk chemotherapy protocols. Even so, about 83% of FN events caused negative outcomes in the patient's treatment plan.

Although age is described in the literature as one of the important risk factors for the development of FN, in the present study, 72% of the patients who developed FN were younger than 60 years, compatible with the age of the highest incidence of sarcomas.

Regarding other known risk factors, the FN events were predominantly observed in patients without comorbidities (68.96%), without skin infection reported (65.51%), and with negative culture (68.96%) to microorganisms.

In cases of afebrile or febrile neutropenia, it is recommended the evaluation of clinical parameters (renal function, liver parameters, infection biomarkers and possible infectious foci) until obtaining an absolute neutrophil count greater than 500 cells/μL. Depending on the criticality, antibiotic therapy may be modified due to the risk of bacteremia.[18] In our study, 13.79% of the events presented alterations in the clinical parameter creatinine, and 89.65% were accompanied by alterations in C-reactive protein.

Several chemotherapy regimens established for the treatment of bone and soft tissue sarcomas have myelosuppressive properties and are used in high doses.[16] In the present study, patients hospitalized due to CIFN were mostly undergoing chemotherapy with high-risk protocols (cisplatin/doxorubicin (20.69%), ifosfamide/etoposide (17.24%), doxorubicin alone (17.24%) and vincristine/doxorubicin/cyclophosphamide (17.24%).

Table 6. Prevalence of CIFN requiring hospitalization and G-CSF use in patients with soft tissues or bone sarcomas.

Chemotherapy protocols	No. of cycles	No.of FN events		% FN[a]
		With G-CSF prophylaxis	Without G-CSF prophylaxis	
Vinblastine D1 E D8	1	0	1	100.00
Carboplatin/Paclitaxel	7	0	2	28.57
Vincristine/ Dactinomycin/Cyclophosphamide[b]	13	1	0	7.69
Ifosfamide/etoposide (D1–D5)	90	5	0	5.56
Vincristine/doxorubicin/Cyclophosphamide[b]	100	5	0	5.00
Doxorubicin/Cisplatin[b]	136	6	0	4.41
Ifosfamide (D1–D3)	140	3	0	2.14
Doxorubicin[b]	266	0	5	1.88
Ifosfamide/Doxorubicin[b]	82	1	0	1.22
Dacarbazine	15	0	0	0.00
Doxorubicin/Vincristine	5	0	0	0.00
Etoposide/carboplatin	5	0	0	0.00
Gemcitabine (D1, D8)	8	0	0	0.00
Gemcitabine (D1, D8, D15)	13	0	0	0.00
Gemcitabine/Docetaxel (D1, D8)	214	0	0	0.00
Irinotecan/dacarbazine (D1, D8)	2	0	0	0.00
Paclitaxel (D1, D15)	118	0	0	0.00
Paclitaxel (D1, D18, D15)	2	0	0	0.00
Paclitaxel weekly	2	0	0	0.00
Topotecan/Cyclophosphamide D1–D5	16	0	0	0.00
vinblastine/methotrexate (D1, D8, D15, D22)	70	0	0	0.00
Vincristine(D1)/Etoposide (D1–D8)	4	0	0	0.00
Vincristine/Cyclophosphamide	37	0	0	0.00
Total	1346	21	8	100.00

[a]To calculate the prevalence, all protocols used in the treatment of bone or soft tissue sarcomas in the 2 years analyzed in the study were considered.
[b]Protocols are classified as high risk (>20%) for the development of FN.
CIFN: chemotherapy-induced FN; G-CSF: granulocyte colony-stimulating factor; FN: febrile neutropenia.

Aoyagi et al. evaluated the occurrence of FN in osteosarcomas and soft tissue cancer patients and reported that protocols with anthracyclines, cisplatin, and ifosfamide increased the risk of developing FN, as observed in our work.[8]

In this work, the management of FN events was mostly performed (86.18%) with antibiotic therapy in the first 24 h, with an empirical regimen of cefepime 2 g intravenously every 8 h. This demonstrated agreement with the ASCO guideline and with the normative service instruction of the analyzed hospital unit. However, it was possible to identify a low adherence (3.44%) to the use of the MASCC risk stratification scale, despite being recommended by the hospital unit and by international guidelines. According to the MASCC scale, patients considered to be at high risk require hospitalization for the management of FN, and patients with low risk can perform FN management in an outpatient setting. Therefore, the low adherence to this tool can lead to unnecessary hospitalizations, causing patient discomfort and increased hospital costs.[12,18]

According to the ESMO and ASCO recommendations, high-risk patients hospitalized with FN should be treated with empiric intravenous therapy with cefepime. However, if they have a previous history of colonization by bacteria with extended-spectrum β-lactamases (ESBL), the use of piperacillin associated with tazobactam or meropenem is recommended. Other cases require specific treatment, such as vancomycin in cases of catheter-focused infections, carbapenems in cases of intra-abdominal infections, and voriconazole or liposomal amphotericin B, depending on the suspected etiologic agent. Patients with the possibility of outpatient treatment (MASSC score greater than 21 points) may receive oral antibiotic therapy with ciprofloxacin associated with amoxicillin with clavulanate, levofloxacin, or moxifloxacin. Low-risk patients who receive initial (first 24 h) empiric intravenous antibiotic therapy may also benefit from cefepime.[12,18,19]

Clinical conditions associated with FN, such as abdominal pain, emesis, diarrhea, lesions in the pubic region, infections of the lower or upper respiratory tract, and mucositis were risk factors found in 58.62% of the cases analyzed in this study and may have corroborated with the high percentage (89.65%) of grade 4 neutropenia (CTCAE).[17]

Hatamabadi et al. reported a high frequency of symptoms such as emesis (16.2%) and diarrhea (34.2%) in patients with breast and gastrointestinal cancer who developed FN, demonstrating similarity with the abdominal/gastrointestinal symptoms found in the present study.[20]

Previous exposure to radiotherapy, identified in 24.13% of FN events, is consistent with the findings of Monuszko

et al. who demonstrated that 24% of patients who developed FN had received radiation along with chemotherapy.[6]

In a study conducted in the United States, the number of hospitalizations for cancer-related neutropenia was 5.2%, and the length of hospitalization was 0 to 7 days.[21] In the present study, approximately 55% of the patients were hospitalized for 5 to 9 days, and those who remained for more than 20 days (6.89%) had associated comorbidities and died.

The prophylactic and therapeutic use of filgrastim is established in the literature. However, due to the risk of adverse events, such as muscle pain, facial flushing, headache, dyspnea, and nausea, the NCCN guideline (2021) recommends non-widespread use in cases of FN.[16] Therefore, it is essential to carry out an analysis of the risk factors associated, such as the presence of associated infection, and the previous prophylactic use of G-CSF, to define the clinical management of FN. As the selection criteria of our study included the use of G-CSF, in all episodes of FN analyzed, the patients used filgrastim, subcutaneously at a dose of 300 mcg/day. Despite the low adherence to the MASCC risk index, the use of filgrastim seems to have been adequate due to the characteristics of the FN events analyzed, 89% of which were grade 4, 28% in patients over the age of 60 years, 41% with a metastatic focus, 34% with sites of infection in the skin and 57% with other associated conditions.

According to NCCN, 2021, patients using filgrastim for the clinical treatment of FN for 1 to 2 days may suffer the impact of adverse reactions without obtaining the therapeutic benefits.[16,22] Our data showed that filgrastim was used for a period of 3 to 4 days in 41.37% of the episodes of FN; however, a pattern of use was not identified, and the treatment intervals ranged from 1 to 10 days, as well as the neutrophil recovery time (> 500 neutrophils/μL) that ranged from 1 to 7 days. It should be noted that the guidelines cited do not have strong recommendations regarding the duration of use of filgrastim in the clinical treatment of FN.

The prevalence of FN events, which requires hospitalization and the use of G-CSF observed during the study period was only 2.15% (29/1346 cases). Among the high-risk protocols (Vincristine/Dactinomycin/Cyclophosphamide, Ifosfamide/Doxorubicin, Doxorubicin, Vincristine/doxorubicin/Cyclophosphamide, and Doxorubicin/Cisplatin) the prevalence of FN ranged from 1.22% to 7.69%.

The isolated doxorubicin protocol showed a low prevalence of FN (1.88%) compared to the others. However, all chemotherapy cycles that triggered this complication were performed without G-CSF prophylaxis. On the other hand, 72.41% (n = 21) of the CIFN cases occurred even with the use of the prophylactic protocol, indicating that the absence of preventive care could generate even more unfavorable outcomes for patients.

Kimura et al. reported a 41.1% incidence of FN in breast cancer patients treated with docetaxel and cyclophosphamide without G-CSF prophylaxis. In the same study, 1.5% of the patients were hospitalized due to FN.[14]

Patients allocated to a high-risk protocol benefit from an individualized approach according to their clinical history and risk stratification, avoiding adverse events and unnecessary hospital costs.[23]

In our analyses, 21 patients, which corresponded to 82.75% of the events identified, suffered impacts on the oncological treatment plan after the FN condition, such as dose reduction (31.03%), delay (20.68%), and/or suspension (17.24%) of chemotherapy treatment. A study of breast cancer patients diagnosed with FN after chemotherapy regimens consisting of doxorubicin/cyclophosphamide/paclitaxel and doxorubicin/cyclophosphamide/docetaxel reported, respectively, that 17.1% and 63.2% of cases required dose reductions in the chemotherapy regimen and that in 14.3% and 10.5% of cases there were delays in chemotherapy treatment.[24] Bacrie et al. reported the need for dose reduction in 25% of patients with breast cancer, and FN associated with chemotherapy regimens similar to those already mentioned.[25]

Differences in the magnitude of the negative impact of FN on the chemotherapy plan can be explained by epidemiological characteristics, tumor type, and chemotherapy protocols. Thus, more studies are needed to perform a more effective comparison.

As a limitation of the study, we can mention the impossibility of correlating the use of G-CSF with the risk stratification of patients using the MASCC scale due to the lack of parameters in the medical records. In addition, the study included only patients diagnosed with FN requiring hospitalization and using G-CSF. Moreover, it is important to emphasize the need for additional data to assess the role of G-CSF prophylaxis in the frequency of FN in patients with soft tissues or bone sarcomas.

Conclusion

Patients with soft tissue or bone sarcomas undergo chemotherapy protocols with myelotoxic properties, which may cause complications such as FN. These neoplasms are low-prevalence tumors, with little data in the scientific literature describing the effects of severe FN in the therapeutic plan of patients. Furthermore, the use of G-CSF for the prophylaxis and treatment of CIFN is controversial in several types of cancer.

The dataset obtained in this study demonstrated that, even with previous G-CSF prophylaxis, high-risk chemotherapy, especially with the presence of doxorubicin, ifosfamide, and cyclophosphamide, was associated with FN requiring hospitalization.

The use of filgrastim in the management of FN should consider the use of myelotoxic protocols, risk factors, and the patient's clinical conditions. In this study, patients had severe or profound neutropenia associated with a clinical history that justified the use of filgrastim.

FN events had negative outcomes with a mortality rate of 7%, and several impacts on the chemotherapy treatment of the patients, generating changes in the chemotherapy protocol,

delays in subsequent chemotherapy cycles, and reduction of chemotherapy doses.

Further studies comparing patients with FN treated with or without G-CSF would be necessary to identify differences in outcomes and more clearly elucidate the clinical relevance of the colony-stimulating factors.

Author's contribution

RTM and LRAM researched literature, conceived the study, and obtained ethical approval. RTM, RCB, MVV, EDB, and LRAM were involved in data acquisition and performed the data analysis. RTM, RCB, and LRAM wrote the first draft of the manuscript. LRAM supervised research. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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