v. 1, n. 5, 2021

International Journal of Health Science

GRANULOCYTE STIMULATION FACTORS IN THE MANAGEMENT OF FEBRILE NEUTROPENIA IN ONCOLOGICAL PATIENTS

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Abstract: Despite advances in the development of targeted cancer therapies, chemotherapy is still the main choice in the treatment of different types of cancer, with the risk of adverse effects, such as febrile neutropenia (NF). Granulocyte-stimulating factors (G-CSF and GM-CSF) emerge as an alternative to regulate the neutrophil count in patients receiving a chemotherapy protocol associated with a high risk of NF. The aim of this work is to carry out a literature review on the use of granulocyte stimulating factors in the management of chemotherapy-induced NF. This is a literature review, using the descriptors "Granulocyte Colony-Stimulating Factor and Chemotherapy-Induced Febrile Neutropenia" in the PubMed database and Google Scholar online platform, generating 4,201 results, of which 7 works, published since 2014 were included. Filgrastim (G-CSF) works by stimulating the proliferation and differentiation of neutrophil progenitors. Furthermore, it induces the phagocytic activity of mature neutrophils and prolongs their survival in circulation. Sargramostim (GM-CSF) stimulates immature granulocytic progenitor cells in the final stage of maturation, also acting on the function of mature neutrophils. Recommended doses are 5 mcg/kg/day for G-CSF and 250 mcg/m2/day for GM-CSF, given subcutaneously. The prophylactic use of filgrastim is indicated from the first treatment cycle for protocols with a high risk of NF (>20%). G-CSF and GM-CSF represent an important tool in the management of chemotherapy-induced NF, which can be used prophylactically in high-risk protocols.
Keywords: Oncology, Filgrastim, Sagramostim, Chemotherapy.

INTRODUCTION

Despite advances in the development of targeted cancer therapies, chemotherapy is still the main choice in the treatment of different types of cancer. Chemotherapy protocols are classified according to the risk of developing febrile neutropenia (NF) as low, intermediate, and high, based on prospective clinical trials of eligible patients. However, such data are difficult to assess, as clinical trials are highly selected and adverse reactions related to treatment toxicity are often underreported. Furthermore, the dose of chemotherapy administered can be very varied and is shown to be directly related to toxicity rates (DALE et al., 2018).

Neutropenia is a serious and common consequence of myelosuppression caused by chemotherapy. Febrile neutropenia can lead to complications that result in the patient's hospitalization and administration of broad-spectrum antimicrobial agents. Therefore, NF becomes a dose-limiting factor for myelosuppressive chemotherapy, which often leads to reductions and delays in treatment cycles, compromising therapy results (LYMAN; ABELLA; PETTENGELL, 2014).

Fever is a typical symptom in patients suffering from chemotherapy-induced neutropenia, however, up to 60%-70% of them will not have a clinically identifiable infection. Gram-positive bacteria are the main causes of infections in onco-hematological patients with febrile neutropenia, and the appearance of resistance of these microorganisms to different drugs is a reason of great concern. More than 50% of pathogens isolated from neutropenic patients, such as Escherichia coli, Pseudomonas aeruginosa and Klebisiella pneumoniae, exhibit resistance to cephalosporins, fluoroquinolones and aminoglycosides. In addition, it is possible to observe an increase in the resistance of these microorganisms to carbapenem, present in about 50% of Enterobacteriaceae isolated in European countries, which is an important risk factor for the mortality of these patients

(ESCRIHUELA-VIDAL, 2019).

Granulocyte-stimulating factors appear as an alternative to regulate the neutrophil count in patients receiving a chemotherapy protocol associated with a high risk of NF. The aim of this work is to carry out a literature review on the use of granulocyte stimulating factors in the management of chemotherapy-induced NF.

METHODOLOGY

With the purpose of contributing to the academic training and updating of health professionals regarding the use of granulocyte stimulation factors in the management of febrile neutropenia in cancer patients, this research used a bibliographic survey in the PubMed database and Google Scholar platform, using the descriptors "*Granulocyte Colony-Stimulating Factor* and *Chemotherapy-Induced Febrile Neutropenia*", associated by the Boolean AND operator, generating approximately 4,201 results. The inclusion criteria were works made available in full, published since 2014, and bibliographies that did not meet the research theme were excluded. Seven articles were selected, 6 in English and 1 in Portuguese.

RESULTS AND DISCUSSION

Granulocyte colony-stimulating factors are glycoproteins that promote the growth and differentiation of neutrophil progenitor cells, in addition to inducing the mobilization of neutrophils from the bone marrow into the bloodstream. They are indicated to prevent and shorten the duration of febrile neutropenia in patients receiving myelosuppressive chemotherapy. The main representatives of this class of drugs are filgrastim (G-CSF) and sargramostim (GM-CSF). Current guidelines recommend primary prophylaxis with filgrastim when the risk of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy is 20% or greater (WANG et al., 2015).

FILGRASTIM (G-CSF)

Short-acting recombinant human G-CSF was first approved in the United States in 1991 and has been used for more than two decades to treat patients worldwide. The pivotal study that led to the approval of filgrastim demonstrated that administration of this drug decreases the incidence, duration, and severity of grade 4 neutropenia, as well as reducing infection rates, patient hospitalization, and duration of treatment with antimicrobial agents in patients with small cell lung cancer (SCLC) treated with myelosuppressive chemotherapy (DALE et al., 2018).

In 2016, filgrastim had 6 Food and Drugs Administration (FDA) approved indications. They are: prevention of chemotherapy-induced neutropenia; reduced time to neutrophil recovery and duration of fever in patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy; reduced incidence and duration of sequelae from severe neutropenia in patients with severe chronic neutropenia (NCS); mobilization of autologous hematopoietic progenitor cells in patients undergoing therapy with peripheral blood progenitor cells; reduced duration of neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation; and increased survival in patients exposed to myelosuppressive doses of radiation. The recommended doses of G-CSF are 5 mcg/kg/day, subcutaneously (AGHEDO; GUPTA, 2021).

SARGRAMOSTIM (GM-CSF)

Unlike filgrastim, which promotes the development of colonies only of granulocytes, sargramostim induces the formation of colonies containing granulocytes and

macrophages (MEHTA; MALANDRA; COREY, 2015). In addition, GM-CSF stimulates immature granulocytic progenitor cells in the final stage of maturation, also acting on the function of mature neutrophils. GM-CSF is currently approved by the FDA to accelerate marrow cell recovery in patients with non-Hodgkin's lymphoma, acute ablastic leukemia, and Hodgkin's disease who have undergone autologous stem cell transplantation. In this type of transplant, the patient's own stem cells are removed from the bone marrow or peripheral blood and stored until the transplant is performed. The patient then undergoes high doses of chemotherapy with the aim of destroying cancer cells. At the end of this process, the stored stem cells are returned to the patient intravenously. Soon after, the administration of GM-CSF is performed in order to reduce the time needed for the neutrophil rates of these patients to be normalized (CALLERA, 2020).

GM-CSF is also indicated after induction chemotherapy in older adult patients with leukemia to decrease the time needed for neutrophil recovery and reduce the incidence of infections, and is also given with the aim of mobilizing hematopoietic progenitor cells for the peripheral blood (MEHTA; MALANDRA; COREY, 2015). The recommended doses of GM-CSF are 250 mcg/m2/day, subcutaneously (AGHEDO; GUPTA, 2021).

CONCLUSION

G-CSF and GM-CSF represent an important tool in the management of chemotherapy-induced febrile neutropenia, which can be used prophylactically in high-risk protocols. They have also been shown to be useful in the recovery of patients undergoing autologous stem cell transplantation. Sargramostim has a broader action than filgrastim, as it is capable of stimulating the differentiation of granulocytes and macrophages, in addition to acting on immature progenitor cells in the final stage of maturation. Therefore, it is possible to conclude that these granulocyte-stimulating factors can play a significant role in the results of antineoplastic therapy, as they avoid reductions and delays in treatment cycles, in addition to reducing the rates of hospitalization and bacterial infections in cancer patients.

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