

Effects of molgramostim, filgrastim and lenograstim in the treatment of myelokathexis

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Abstract Myelokathexis is a very rare form of chronic hereditary neutropenia resulting from impaired neutrophil releasing mechanism in the bone marrow. The recombinant human granulocyte-macrophage (molgramostim) and granulocyte (filgrastim, lenograstim) colony stimulating factors release the mature granulocytes from the bone marrow. We describe a 43-year-old woman suffering from myelokathexis, with the absolute neutrophil count ranging between 0.03 and $1.35 \times 10^9/L$. In the period before the introduction of cytokines, the patient had more than 80 major infectious episodes. Since 1991, infections in this patient have been treated with cytokines, given in conjunction with antibiotics. Initially, she received molgramostim in a daily dose of $5 \mu g/kg$ subcutaneously, which stimulated the release of granulocytes from her bone marrow, thereby allowing successful treatment of infection. After the development of hypersensitivity, molgramostim was substituted with filgrastim. Finally, lenograstim was given a trial. With all three cytokines, the patient's neutrophil count always attained normal values already 4 hours after subcutaneous application of the drug in a dose of $5 \mu g/kg$, the highest neutrophil levels were measured at 24 hours post-injection, and the neutrophil count was again close to the baseline value 72 hours after the treatment. A slight neutropenia was present 48 hours after the application of filgrastim. We believe that all three cytokines are equally effective in increasing the neutrophil count in venous blood of patients with myelokathexis.

Key words neutropenia · treatment · cytokines · GM-CSF · G-CSF

Introduction

Myelokathexis is a very rare form of chronic hereditary neutropenia first described by Zuelzer [8] and Krill [4] in 1964. The characteristics of myelokathexis include a bone marrow myeloid hyperplasia with numerous mature neutrophils having cytoplasmic vacuoles, heavy granulation,

hypersegmentation, and pyknotic nuclear lobes connected by thin filaments. Mature granulocytes are retained in the marrow (kathexis=retention), where they undergo degenerative changes.

Myelokathexis occurs more often in females and frequently affects multiple members of a family. Patients have a lifelong history of severe neutropenia and recurrent infections. Transient elevation of neutrophil counts has been reported in association with infection, corticosteroids, adrenaline, and recombinant human granulocyte-macrophage (GM-CSF) and granulocyte (G-CSF) colony stimulating factors [3]. GM-CSF (molgramostim) and G-CSF (non-glycosylated filgrastim, glycosylated lenograstim) stimulate the proliferation of committed stem cells, their maturation into mature granulocytes and their release from the bone marrow.

In this paper, we describe the management of a female patient with myelokathexis and the effect of cytokines on her absolute neutrophil count (ANC). The effects of molgramostim and filgrastim were studied during upper respiratory tract infections. The response to lenograstim was tested during an infection-free period.

Case report

Our patient is one of the two siblings with myelokathexis who were described in the literature in 1981 [2]. She is now 43 years old. She has a rather severe form of the disorder, with the ANC ranging between $0.03 \times 10^9/L$ and $1.35 \times 10^9/L$. In the period before the introduction of cytokines, the patient had more than 80 major infectious episodes. Since 1991, infections in this patient have been treated with cytokines, given in conjunction with antibiotics. Initially, she received molgramostim (Leucomax) subcutaneously in a daily dose of $5 \mu g/kg$, which stimulated the release of granulocytes from her bone marrow, thereby allowing successful treatment of infection. Peak ANC values ($11.1 \times 10^9/L$) were observed at 24 hours post-injection.

We later evaluated the neutrophil kinetics during a 5-day course of molgramostim administered subcutaneously in daily doses of $5 \mu g/kg$ during an infection-free period. The patient's ANC increased from $0.3 \times 10^9/L$ at baseline to $8.7 \times 10^9/L$ at 24 hours after the first dose. In the following

4 days it ranged between $4.1 \times 10^9/L$ and $6.6 \times 10^9/L$. At 24 hours after the last injection, the ANC was $6.3 \times 10^9/L$, and over the following 24 hours it decreased to $0.6 \times 10^9/L$. On the basis of these results, an alternate day dosing regimen was introduced for the treatment of infections.

In 1992, the patient developed hypersensitivity to molgramostim, manifested by suffocation, redness and itching of the skin, and pain in the lumbar region. Consequently, molgramostim was substituted with filgrastim (Neupogen), administered subcutaneously in a dose of $5 \mu g/kg$ on alternate days. Finally, lenograstim (Granocyte 34) was given a trial, the dose being the same as with the previous two drugs. The patient's neutrophil count always attained normal values already 4 hours after application of cytokines (Fig. 1). The highest neutrophil levels were measured 24 hours after the first injection ($11.1 \times 10^9/L$ after molgramostim, $18.6 \times 10^9/L$ after filgrastim, and $11.8 \times 10^9/L$ after lenograstim). A slight neutropenia was noted 48 hours after application of filgrastim. With all three cytokines, the neutrophil count was always close to the baseline value 72 hours after the end of treatment.

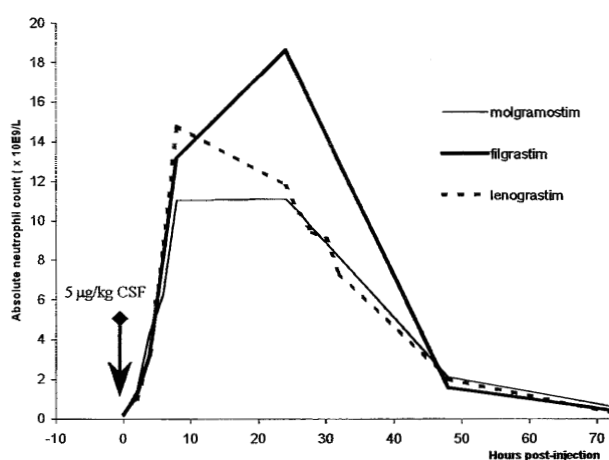


Fig. 1 Neutrophil response to single injection of molgramostim, filgrastim or lenograstim

Discussion

Prior to the advent of haematopoietic growth factors, antibiotics were the only accepted therapy for infections in patients with myelokathexis. Treatment with molgramostim [1, 2], filgrastim [3, 7] or lenograstim has been shown to enhance the release of mature myeloid cells into peripheral blood, thereby allowing successful treatment of infection.

Our patient always experienced a rapid rise in the number of circulating neutrophils within 8 hours of application of cytokines. Such a rapid increase in ANC can most probably be explained by a release of neutrophils from the bone marrow

storage pool due to the neutrophil releasing activity of cytokines. The increase in ANC observed in our patient after the application of molgramostim and filgrastim was greater than in the other patients described in the literature [3]. This may be due to a greater pool of myeloid cells present in the bone marrow of our patient as compared to the others, differences among the patients in their response to infection, or the presence of multiple abnormalities of granulocyte function in the other patients.

The mechanism by which pharmacological levels of cytokine stimulate the release of granulocytes is unknown. Speculation regarding the etiology of myelokathexis has included haematopoietic cytokine deficiencies, qualitative abnormalities of haematopoietic cytokines, abnormal cytokine receptors, leukocyte adhesion abnormalities, and accelerated apoptosis [7].

When cytokines were given to our patient in repeated doses at 1- or 2-day intervals, the greatest ANC increase was always observed after the first dose. This is understandable since the first cytokine dose caused the mature granulocytes stored in the bone marrow to be released into the peripheral blood. When filgrastim was applied on alternate days, the ANC values at 48 hours post-injection ranged from $1.5 \times 10^9/L$ to $3.6 \times 10^9/L$. Glycosylated and non-glycosylated G-CSF have been shown to differ in their effect on the neutrophil count [6], but in our patient the difference in the ANC increase observed after the application of filgrastim and lenograstim was insignificant.

On the basis of our experience we believe that all three cytokines are equally effective in increasing the neutrophil count in venous blood of patients with myelokathexis.

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