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Febrile neutropenia prophylaxis with short- and long-acting granulocyte colony-stimulating factors during treatment of solid tumours

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ABSTRACT

Haematological toxicity of chemotherapy is a very important problem in oncology. The introduction of granulocyte colony-stimulating factor (G-CSF) into clinical practice is one of the most important breakthrough moments in supportive care. The use of G-CSF allows to reduce the risk of febrile neutropenia and maintain the intensity of oncological treatment, so increases not only the safety, but also the effectiveness of cancer therapy. The application of biosimilars, including biosimilar filgrastim and pegfilgrastim, was another important step that made it possible to increase access to modern biological medicines.

Key words: neutropenia, febrile neutropenia, short-acting granulocyte colony-stimulating factors, long-acting granulocyte colony-stimulating factors, biosimilars

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Introduction

Haematological toxicity remains one of the most common side-effects of chemotherapy. Neutropaenic fever as a potentially fatal complication is still a very significant problem in cancer patients. The introduction of filgrastim into clinical practice (followed by long-acting granulocyte colony-stimulating factors [G-CSFs]) was one of the most important breakthroughs in oncological supportive care and gave oncologists a tool with which to use systemic treatment safely and more effectively. The introduction of biosimilars, including bioequivalent filgrastim and pegfilgrastim, was another important step that increased the availability of modern biological drugs.

G-CSF in the prevention of neutropaenic fever

Granulocyte colony-stimulating factor (G-CSF) is a natural cytokine that stimulates haematopoietic progenitor cells, leading to increased production and release of neutrophils from the bone marrow and prolonging their survival. The history of clinical studies assessing the activity and safety of filgrastim in cancer patients receiving chemotherapy dates back to 1988 [1]. The main indication for the use of G-CSF preparations is prevention of neutropaenic fever. It is recommended that G-CSF be used for primary prevention in situations where the risk of neutropaenic fever is 20% or higher. This recommendation appears in both national (Polish

Society of Clinical Oncology [2]) and international guidelines, including ESMO (European Society of Medical Oncology [3]), ASCO (American Society of Clinical Oncology [4]), and NCCN (National Comprehensive Cancer Network) [5]. The basic determinant of risk level is the chemotherapy regimen used. When chemotherapy regimens with a 10–20% risk of neutropaenic fever are used, G-CSF in primary prevention may be considered in the presence of other factors predisposing to this complication, which are:

- age \geq 65 years;
- advanced cancer;
- an earlier episode of neutropaenic fever;
- impaired general condition (ECOG \geq 2);
- impaired nutritional status (albumin $<$ 35 g/L);
- concomitant diseases (the risk increases with the number of diseases), in particular cardiovascular diseases;
- response to treatment (the highest risk in patients who did not experience disease remission, the lowest risk if complete response is achieved);
- inflammation of mucous membranes (mucositis) lining the mouth and/or gastrointestinal tract (severity and duration of mucositis impact the risk).

Secondary prophylaxis (after a previous episode of neutropaenic fever) includes the prevention of subsequent episodes as well as a reduction in the time of neutropaenia, which may affect the delay of subsequent chemotherapy cycles. Secondary prophylaxis should be considered, especially if delayed systemic treatment or dose reduction might have a significant impact on the effectiveness of treatment. This situation primarily concerns radical treatment, where maintaining the right dose intensity can affect the probability of cure. Obviously, this does not exclude the use of G-CSF in secondary prevention in patients undergoing palliative treatment. Each decision should be individualised and analysed in the context of a specific clinical situation.

There are a number of clinical studies and several meta-analyses as well as systematic reviews summarising the benefits of using G-CSF in the prevention of neutropaenic fever. The meta-analysis by Kuderer et al. summarised the results of 17 randomised clinical trials (including one assessing the effectiveness of pegylated form), which involved in total 3493 patients. The analysis showed a significant reduction in the risk of neutropaenic fever (RR 0.538, 95% CI 0.430–0.673), infection-related mortality (RR 0.552, 95% CI 0.338–0.902), and early mortality for any reason during chemotherapy (RR 0.599, 95% CI 0.433–0.830). In the group of patients receiving prophylactic G-CSF, it was possible to maintain the assumed dose intensity on average 95.1% (range 71.0–95.0%), while among patients receiving placebo it was 86.7% (91.0–99.0%). This difference was statistically significant ($p < 0.001$) [6].

Another meta-analysis published in 2005 by Clark et al. Included 13 studies (1569 patients). It showed shortening of hospitalisation among patients receiving primary G-CSF prophylaxis (HR 0.63, 95% CI 0.49–0.82, $p = 0.0006$) and shortening of the time to return neutrophil levels to their baseline (HR 0.32, 95% CI 0.23–0.46, $p < 0.0001$). There was a boundary statistical significance regarding risk reduction of infection-related death (OR 0.51, 95% CI 0.26–1.00, $p = 0.05$) and a statistically insignificant reduction in overall mortality (OR 0.68, 95% CI 0.43–1.08, $p = 0.1$) [7].

Long-acting G-CSFs

Given the short half-life of filgrastim and the associated necessity of daily administration, attempts have been made to chemically modify the molecule to extend the elimination time.

Pegfilgrastim is a modified filgrastim molecule. The modification involves the binding of polyethylene glycol (PEG) to the filgrastim molecule at the N-terminus of the polypeptide chain. Modification of the molecule does not affect the interaction with G-CSF receptor and the biological function of the drug. Considering the size of the PEG component (approx. 20 kDa), the drug is practically not subject to renal clearance. Elimination is mainly based on neutrophil clearance (it involves internalising the drug after binding to the G-CSF receptor) [8]. This mechanism is specifically self-regulated; the serum concentration of the drug decreases more slowly during the nadir, while the elimination of the drug is accelerated during the period of increase in neutrophil levels. The bioavailability of the drug is 60–70%. After subcutaneous administration, it is slowly absorbed, and the maximum drug concentration occurs after 1–2 days. Due to the half-life (approx. 15–80 hours vs. 110 minutes for filgrastim), a single drug administration does not have to be repeated in the following days and constitutes full treatment for one cycle of chemotherapy.

Pegfilgrastim was registered by the FDA (Food and Drug Administration) and EMA (European Medicines Agency) in 2002. The drug was the subject of two pivotal phase III studies in which the effectiveness of a single dose of pegfilgrastim was compared with repeated daily administration of filgrastim. In the first study, a group of 310 breast cancer patients receiving chemotherapy based on doxorubicin and docetaxel were analysed. There were no significant differences in reducing the duration of neutropaenia (1.7 days for pegfilgrastim and 1.8 days for filgrastim), while the incidence of neutropaenic fever was lower in the pegfilgrastim group (9% and 18%, respectively) [9]. In the second of these studies, a group of 157 patients receiving a similar chemotherapy regi-

men (doxorubicin with docetaxel) was analysed. Similar duration of grade 4 neutropaenia was observed in both arms (1.8 and 1.6 days), while the incidence of febrile neutropaenia was 13% and 20%, respectively [10]. In a study by Vogel et al. the effectiveness of pegfilgrastim prophylaxis was compared with placebo in a group of 928 patients treated with docetaxel alone. The drug was significantly more effective in the analysis of endpoints such as the frequency of neutropaenic fever (1% vs. 17%, $p < 0.001$), the frequency of hospitalisations associated with neutropaenic fever (1% vs. 14%, $p < 0.001$), and the use of intravenous antibiotics (2% vs. 10%, $p < 0.001$) [11].

Another long-acting form of G-CSF (registered in the European Union but not in the US) is lipegfilgrastim, in which the filgrastim molecule undergoes modification involving binding to methoxypolyethylene glycol via a carbohydrate linker (glycopegylated form of filgrastim). The effectiveness of lipegfilgrastim was assessed in two pivotal phase III studies. In the first study (XM22-03) the drug was used in the prophylaxis of neutropaenia in 202 breast cancer patients undergoing chemotherapy with doxorubicin and docetaxel. There were no significant differences in the incidence of severe neutropaenia ($ANC < 0.5 \times 10^9/L$) and the duration of neutropaenia both in the first and subsequent treatment cycles [12]. Another study (XM22-04) compared the effectiveness of prophylactic lipegfilgrastim with placebo. The study included 375 patients with non-small cell lung cancer receiving chemotherapy according to the EP regimen. The primary endpoint, a statistically significant reduction in the frequency of neutropaenic fever after the first cycle of chemotherapy, was not achieved. The study, however, showed greater effectiveness of the drug in reducing the duration of deep neutropaenia and the depth of nadir [13].

Comparison of effectiveness between short- and long-acting drugs

A number of studies have been published comparing the efficacy of short- and long-acting G-CSF preparations. Available data are conflicting; although some results indicate higher effectiveness of pegfilgrastim, others do not confirm this observation. A meta-analysis by Pinto et al. was aimed at a comparison of the effectiveness of a single dose of pegfilgrastim with the daily dosage of filgrastim (the number of filgrastim doses per chemotherapy cycle was 10–14). Five clinical trials were included in the analysis, in which 617 patients participated. Analysis showed a higher efficacy of pegfilgrastim in the prevention of neutropaenic fever (RR 0.64, 95% CI 0.43–0.97) [14]. Another meta-analysis (Cooper et al.) showed similar results; it evaluated the effectiveness of G-CSFs in patients undergoing chemotherapy for

solid and haematological cancers. In total, 20 studies comparing the effectiveness of primary prevention with a lack of prevention were included in this meta-analysis ($n = 4710$). The meta-analysis showed a statistically significant 49% reduction (95% CI 0.41–0.62) of the relative risk of neutropaenic fever, with relative risk 0.57 (0.48–0.69) for filgrastim and 0.30 for pegfilgrastim (0.14–0.65). In some studies (5) included in the analysis, the effectiveness of pegfilgrastim and filgrastim was compared, which in a combined analysis led to a statistically significant difference in favour of its long-acting form (HR 0.66, 95% CI 0.44–0.98) [15]. In turn, a meta-analysis by Cornes et al. showed no significant difference in preventing febrile neutropaenia between long- and short-acting drugs (although numerically it was a small difference in favour of long-acting molecules [RR 0.86, 95% CI 0.68–1.10]), while it indicated an advantage of long-acting drugs both in preventing the reduction of cytotoxic drug dosage (RR 0.69, 95% CI 0.57–0.83) as well as delays in their administration (RR 0.70, 95% CI 0.62–0.79) [16]. It is difficult to say unequivocally whether these differences are due to the actual higher efficacy of long-acting forms of G-CSF or rather to the use of an overly low total dose of short-acting drugs (it is estimated that a single administration of pegfilgrastim 6 mg is equivalent to 11 administrations of filgrastim [17, 18]). The latter scenario seems more likely.

Adverse events

The most common side effects related to the use of filgrastim (including long-acting forms) are transient flu-like symptoms (osteoarticular and muscle pain, occurrence of low-grade fever, less often fever). These symptoms are usually mild to moderate and resolve without intervention. They can be relieved with the use of painkillers and anti-inflammatory drugs. In the meta-analysis by Kuderer et al. the aforementioned symptoms were reported in 10.4% of patients in the control group (receiving placebo) and in 19.6% of patients in the group receiving G-CSF (RR 4.023, 95% CI 2.156–7.52) [6]. In turn, one of the parameters assessed in the previously mentioned meta-analysis by Pinto et al. was the difference in the frequency of flu-like symptoms among patients receiving short- and long-acting forms of G-CSF. This analysis showed no statistically significant differences between pegfilgrastim and filgrastim with respect to this parameter (RR 0.95, 95% CI 0.76–1.19) [14].

Secondary cancers

There are reports indicating a relationship between the use of G-CSF and an increased risk of secondary

cancers: acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS). A meta-analysis by Lyman et al. in 2018 included 68 clinical trials comparing the effects of using filgrastim with no G-CSF supportive treatment. An increased risk of secondary cancers (AML, MDS) was shown in patients receiving G-CSF (RR 1.85, 95% CI 1.19–2.88). However, the use of G-CSF translated into an extension of overall survival for the entire analysed population (RR 0.92, 95% CI 0.90–0.95). An even greater benefit was found in the group of patients receiving dose-dense regimens (RR 0.86, 95% CI 0.80–0.92) [19]. The authors highlighted that the risk of secondary cancer induced by cytostatics exceeds the values found for G-CSF, and the potential risk is balanced by improved survival (probably resulting from maintaining higher intensity of cytostatics doses among patients receiving G-CSF).

Biosimilars

G-CSF preparations belong to the group of biological drugs (biopharmaceuticals) manufactured with the use of biotechnology. The main difference between biopharmaceuticals and “classic” drugs is the way they are produced. Biopharmaceuticals are most often macromolecular proteins of high complexity and complicated spatial structure. They are produced in bioreactors by genetically modified organisms or cell lines, e.g. *Escherichia coli* (like G-CSF), yeast *Saccharomyces cerevisiae*, or modified mammalian cell lines (e.g. Chinese hamster ovary [CHO] cells).

As in the case of small molecules, the expiry of the patent protection for innovative biotechnological drugs gives the possibility to market of their counterparts — biosimilars. With respect to classic small molecule drugs that are products of chemical synthesis, the situation is definitely easier because the generic drugs are the molecules with identical structure and properties. Considering the production method, the situation is much more complicated for biopharmaceuticals and biosimilars. Therefore, the registration requirements set by authorities for manufacturers of biosimilars are more complex than for generic medicines.

The first biosimilar preparations of filgrastim (bioequivalent to the reference drug Neupogen®) were registered by the European Medicines Agency in 2008 and found a permanent place in everyday clinical practice. There are currently seven biosimilar filgrastim preparations registered in Europe (Accofil®, Filgrastim Hexal®, Grastofil®, Nivesitim®, Ratiograstim®, Tevagrastim®, and Zarzio®).

A completely new phenomenon is the appearance of biosimilar preparations of pegfilgrastim (the original drug Neulasta®). The first drugs were registered in Europe in September 2018. Currently, six drugs from this group are registered (Fulphila®, Grasustek®, Pelgraz®,

Pelmeg®, Udenyca®, and Ziextenzo®). Some of these drugs were registered on the basis of studies involving healthy volunteers. However, there are four phase III studies assessing the efficacy and safety (bioequivalence) of pegfilgrastim biosimilars in the population of patients treated with cytostatics due to breast cancer.

The biosimilar drug MYL-1401H (Fulphila®) was evaluated in a phase III study of breast cancer patients receiving combination chemotherapy (docetaxel, doxorubicin, and cyclophosphamide) in the first-line treatment. Patients were randomly assigned in a 2:1 ratio to study arms (MYL-1401H vs. the reference drug Neulasta®). There were no significant differences in the primary endpoint (mean duration of neutropenia $< 0.5 \times 10^9/L$ after the first chemotherapy cycle), which was 1.2 days (± 0.93) and 1.2 days (± 1.10), respectively. The analysis of secondary endpoints (including the frequency of adverse events) also showed bioequivalence of both drugs [20].

The bioequivalence of Grasustek® (RGB-02) was evaluated in a randomised, double-blind phase III study in a group of 239 breast cancer patients receiving chemotherapy based on doxorubicin and docetaxel. The efficacy of the study drug was compared with the reference drug (Neulasta®), and patients were assigned to both arms in a 1:1 ratio. There were no differences in the primary endpoint, which was the duration of neutropenia $< 0.5 \times 10^9/L$ after the first treatment cycle (1.7 vs. 1.6 days). Similarly, no statistically significant differences were found in the secondary endpoints (e.g. duration of neutropenia after subsequent treatment cycles and frequency of neutropaenic fever) [21].

Ziextenzo® (LA-EP2006) was evaluated in two phase III studies: PROTECT-1 and PROTECT-2 [22, 23]. Both studies showed bioequivalence to the reference drug (Neulasta®). Furthermore, Blackwell et al. published a pooled analysis of both studies confirming the conclusions of each of them. Both studies included 624 breast cancer patients receiving neoadjuvant or adjuvant chemotherapy according to the TAC regimen (docetaxel, doxorubicin, and cyclophosphamide). Patients were randomised in a 1:1 ratio. Regarding the primary endpoint (duration of neutropenia $< 0.5 \times 10^9/L$ after the first treatment cycle), there were no significant differences between the two drugs (1.05 ± 1.055 days for LA-EP2006 and 1.01 ± 0.958 days for Neulasta®). Bioequivalence was also demonstrated in the analysis of secondary endpoints (regarding both efficacy and safety in the first and subsequent chemotherapy cycles) [24].

Conclusions

The use of G-CSF allows the reduction of the risk of neutropaenic fever, as well as maintenance of the intensity of treatment by sustaining scheduled chemo-

therapy, which directly affects not only the safety but also the effectiveness of cancer therapy. The high cost of biopharmaceuticals has become one of the drivers of the biosimilar drug industry. As in the case of “classic” drugs, where the introduction of generic preparations has reduced their prices, biosimilars have decreased the cost of cancer treatment using biopharmaceuticals. As a result, it has increased the availability of modern biological medicines obtained thanks to innovative technologies.

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