

Risks of haematological malignancies in patients treated for solid tumours associated with the use of pegylated granulocyte colony-stimulating factors: A single centre study since 2005

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Abstract. The use of pegylated granulocyte colony-stimulating factors (PGCSFs), specifically pegfilgrastim and lipegfilgrastim, has been widely adopted to reduce the incidence of febrile neutropenia in patients undergoing chemotherapy. However, concerns regarding the long-term safety of PGCSFs, particularly the risk of secondary haematological malignancies, remain. The present study aimed to evaluate the incidence of secondary haematological malignancies in patients treated for solid tumours with PGCSFs at a single institution from 2005 to 2019. A retrospective analysis was conducted using an electronically managed database of 1,577 patients who received PGCSFs during chemotherapy for solid tumours. Patients with a history of any granulocyte or granulocyte-macrophage colony-stimulating factor administered prior to PGCSF were excluded. The incidence of secondary malignancies was assessed from the first application of PGCSF until the last patient contact, with a maximum

follow-up time until December 2023. Among the evaluated cohort of 1,577 patients with the median follow-up time of 4.75 (0.0-18.1) years, respectively, with 757 (36.4%) patients followed-up for ≥ 5 years and 203 (18.1%) patients for ≥ 10 years; 7 (0.44%) patients were diagnosed with secondary haematological malignancies, including myelodysplastic syndrome in 2 patients, multiple myeloma in 3 patients and non-Hodgkin lymphoma in 2 patients. The present study findings demonstrated that the long-term use of PGCSFs in patients treated for solid tumours does not substantially increase the risk of secondary haematological malignancies, which supports their safety profile in clinical practice. However, a longer follow-up is necessary to further evaluate the safety of PGCSFs, particularly for biosimilars.

Introduction

Pegfilgrastim (PF) and lipegfilgrastim (LF), both pegylated granulocyte colony-stimulating factors (PGCSFs), are recommended and widely used to reduce the incidence of febrile neutropenia (FN). This occurs by prolonged stimulation of the proliferation, differentiation, and activation of neutrophil precursors in the bone marrow through binding to the G-CSF receptor following high-risk chemotherapy (CHT) in a variety of cancer types, such as breast cancer, lymphomas, sarcomas and gynaecological cancers, with broader utilisation to mitigate the risk of FN during the COVID-19 pandemic by preventing or shortening the duration and severity of neutropenia (1-8). The Delphi expert consensus also supports the use of PGCSFs in primary and secondary prophylaxis to maintain CHT intensity in CHT regimens with the potential to induce severe neutropenia ($\leq 0.5 \times 10^9/l$) (1). Biosimilar pegfilgrastim and filgrastim molecules are considered as effective and safe as their originator products (1-5). In terms of adherence and reported use by the patients, there is a guidelines-based preference for PGCSFs, which are administered once per chemotherapy cycle, over filgrastim, a short acting G-CSF, which requires daily injections for 10-14 days (1,6).

A meta-analysis of 8 clinical and 3 observational studies, which encompassed 1,303 high-risk patients, demonstrated

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Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BEP, bleomycin + etoposide + cisplatin; CHT, chemotherapy; AC, doxorubicin + cyclophosphamide; TAC, AC + docetaxel; FN, febrile neutropenia; FEC, fluorouracil + epirubicin + cyclophosphamide; GCSF, granulocyte colony-stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; HGS, high grade serous; LF, lipegfilgrastim; MDS, myelodysplastic syndrome; PC, paclitaxel + carboplatin; PF, pegfilgrastim; PGCSFs, pegylated GCSF; RT, radiotherapy

Key words: pegfilgrastim, lipegfilgrastim, pegylated granulocyte colony-stimulating factor, secondary haematological malignancies, supportive care

that prophylactic PF significantly reduced FN incidence (5 vs. 29%, $P<0.0001$), with a benefit observed in patients aged ≥ 65 years (9,10). Similarly, in the NADIR and LEOS observational studies, prophylactic LF reduced the incidence of FN to 2 and 2.4%, respectively (11,12). LF and PF have demonstrated comparable efficacy in reducing severe neutropenia and FN in patients with breast cancer receiving adjuvant doxorubicin/docetaxel CHT (13,14) and in patients with aggressive B-cell NHL treated with CHOP-21, with an FN incidence of 2% after either LF or PF prophylaxis (15).

While PGCSFs are generally considered safe, their long-term safety profile, particularly regarding secondary haematological malignancies, remains a topic of ongoing discussion. The incidence of secondary haematological malignancies in patients treated for solid tumours is complex, with varying estimates and contributing factors, such as the type of CHT used, radiotherapy and individual genetic predispositions; however, the potential leukaemogenic effect of GCSFs is a subject of controversy (16-22). Real-world data are key for verifying the long-term safety of these medications in everyday clinical practice. The present study therefore aimed to conduct a large retrospective analysis to address these concerns and further evaluate the safety of PF and LF with respect to the incidence of secondary haematological malignancies.

Materials and methods

A retrospective analysis of an electronically managed database of drug administrations and patients registered at Charles University Hospital (Pilsen, Czech Republic) since 2005 (first application of PF in September 2005) was performed, with maximum follow-up until December 2023. The present analysis included only adult patients treated for solid tumours with CHT supported with the administration of PF or LF. Patients with haematological malignancies and patients with any granulocyte or granulocyte-macrophage colony-stimulating factor administered in their history prior to PGCSF administration were excluded from the present study. The incidence of haematological malignant neoplasms was evaluated within the period of the first application of PGCSF until the last contact with each patient. Statistical univariate analyses (Fisher's exact test two-tailed) were performed using the GraphPad Prism 10 Software (Dotmatics) to compare incidence of secondary haematological malignancy in patients treated with PF and LF, and patients with breast cancer and with other malignancies. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 1,577 consecutive patients with solid malignancy, who had ≥ 1 application of PGCSF in the period of September 2005 to December 2019 and no evidence of any previous application of granulopoiesis growth factor in their history, were assessed and evaluated. From 2005-2010, PGCSFs were administered to 214 (13.6%) patients; from 2011-2015 to 537 (34.1%) patients; and from 2016-2019 to 826 (52.3%) patients.

The PGCSFs administered included PF originator (Neulasta®; Amgen, Inc.), PF biosimilar (Pelgraz; Accord Healthcare) and LF (Lonquex; Teva Pharmaceutical Industries, Ltd.). PF originator was administered in 1,218 (77.3%) patients

Table I. Characteristics of patients (n=1,577) from 2005-2019 and PGCSF use.

Characteristics	Patients, n (%)
Age, median (range), years	54 (18-84)
Sex	
Female	1,116 (71.0)
Male	461 (29.0)
Type of cancer	
Breast	751 (47.6)
Gastrointestinal (C15-20)	204 (12.9)
Germinal	185 (11.7)
Tubo-ovarian	123 (7.7)
Pancreatic cancer	50 (3.1)
Uterus (C53-54)	50 (3.1)
Sarcomas	40 (2.5)
Urinary tract	35 (2.2)
Head and neck	34 (2.2)
Prostate	23 (1.4)
Other	82 (5.1)
PGCSF molecule	
PF originator	1,218 (77.3)
PF biosimilar	143 (9.0)
LF original	216 (13.7)
Sequence of molecules when using different PGCSF ^a	
PF originator changed to LF	54 (32.5)
PF originator changed to PF biosimilar	49 (29.5)
LF changed to PF originator	33 (19.8)
LF changed to PF biosimilar	18 (10.8)
PF biosimilar changed to LF	12 (7.2)
PF biosimilar changed to PF originator	0 (0.0)

^an=166. PGCSF, pegylated granulocyte colony-stimulating factors; PF, pegfilgrastim; LF, lipegfilgrastim.

from September 2005-April 2019; PF biosimilar in 143 (9%) patients from March-December 2019; and LF in 216 (13.7%) patients from August 2014-December 2019.

Reuse of the same or different PGCSFs in a subsequent chemotherapy line, or a change to a different PGCSF molecule within the same treatment line (i.e. PF originator changed to PF biosimilar, or PF biosimilar changed to LF) was observed in 179 patients. Of these, 166 received a different PGCSF molecule than the original one (Table I). In a total of 18 patients, the consecutive use of PF originator, PF biosimilar and LF was observed during their overall oncological treatment. At the time of evaluation in December 2023, the median time of follow-up was 57 (0.25-217) months, 4.75 (0-18.1) years, respectively, with 757 (36.4%) patients followed -up for ≥ 5 years and 203 (18.1%) patients for ≥ 10 years. A total of 629 (39.8%) patients were alive (39.8%) at the time of the last follow-up in December 2023, 749 (47.6%) had died and 199 (12.6%) had been lost to follow-up.

Table II. Secondary haematological malignancy incidence by PGCSF type and tumour.

PGCSF molecule	No. of patients with secondary haematological malignancy	Type of secondary haematological malignancy	Type of primary tumour	P-value ^b
PF originator (n=1,218)	7	Multiple myeloma ^a (n=2) Gastric diffuse large B-cell lymphoma (n=1) Follicular lymphoma (n=1) Myelodysplastic syndrome with AML transformation (n=1) Myelodysplastic syndrome with pancytopenia (n=1) Multiple myeloma ^a (n=1)	Breast cancer (n=5) Ovarian cancer (n=1) Germinal tumour seminoma (n=1)	-
PF biosimilar (n=143)	0	-	-	>0.999
LF original (n=216)	0	-	-	0.6

^aTotal multiple myeloma cases=3. ^bCompared with PF originator. -, not applicable; PGCSF, pegylated granulocyte colony-stimulating factors; PF, pegfilgrastim; LF, lipegfilgrastim; AML, acute myeloid leukaemia.

Within the cohort of 1,577 patients, a total of 7 haematological malignancies were diagnosed (0.44%) during the follow-up period. In total, 2 patients were diagnosed with myelodysplastic syndrome, 3 patients with multiple myeloma and 2 patients with non-Hodgkin lymphoma (Table II and III). All cases with haematological malignancy development were observed in the cohort of patients treated with PF originator (PF originator 7/1,218 vs. PF biosimilar 0/143, $P<0.999$; PF originator 7/1,218 vs. LF 0/216, $P=0.6$). In total, 5 out of 7 patients that developed haematological malignancies were treated for breast cancer in their history; of the total cohort, haematological malignancies developed in 5 out of 751 (0.66%) patients with breast cancer. The difference in the incidence of secondary haematological malignancies between patients with breast cancer (0.66%) and patients with other malignancies (0.24%) was not statistically significant (patients with breast cancer 5/751 vs. other malignancies 2/826; $P=0.26$). It is important to note that one patient had a proven germline mutation in *PALB2* (c.3256C>T) (Table III).

Discussion

PGCSFs represent an important component of complex supportive care in patients treated with chemotherapy for solid tumours. While biosimilar PF is considered to have comparable efficacy and safety to its originator product, despite LF not having a biosimilar counterpart, further observations and long-term safety monitoring are recommended (1-5). However, the leukaemogenic effect of granulocyte or granulocyte-macrophage colony-stimulating factor (GCSF or GMCSF) remains a subject of controversy. Several observational studies have suggested that patients with cancer receiving CHT and supportive care with GCSF or GMCSF have a greater incidence of acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) compared with those not receiving such

growth factors (16-18). However, the results of subsequent reviews and meta-analyses of randomised controlled trials of CHT with and without GCSF or GMCSF reported that growth factor support enables the administration of a greater relative dose intensity of chemotherapeutic agents compared with CHT without GCSF or GMCSF, and greater dose intensity is known to be leukaemogenic, which potentially explained the small increase in the risk of secondary malignancies reported in the previous studies, but suggested that this risk was balanced by improvements in overall survival, reduced cancer recurrence and reduced occurrence of fatal infections (20-22).

In a previous cohort study of 439,704 patients, a total of 3,046 cases (0.69%) of haematologic malignancies occurred; breast cancer survivors had significantly higher standardised incidence rates of AML and MDS compared with that of women in the general population. A slight increase in the incidence of multiple myeloma and acute lymphoblastic leukaemia (ALL) was also reported (19). In a study of 122,373 breast cancer survivors, 781 cases of haematologic malignancies occurred (0.63%), an increase was observed in the risk of AML and MDS among patients treated with chemotherapy plus GCSF compared with chemotherapy alone although this was not statistically significant, and a significant increase in the risk of ALL was observed with increasing cycles of GCSF (≥ 4 doses; hazard ratio, 2.3; 95% CI, 1.0-5.1) (16).

Therefore, the results of the present analysis aligned with the aforementioned studies. Overall, of the present study cohort (n=1,577), haematological malignancy developed in 0.44% (n=7), with a marked increase in the group of patients with breast cancer (n=751), with the incidence of 0.66% (n=5). Although the incidence was higher in patients with breast cancer in both absolute and relative numbers, this difference was not statistically significant. Thus, the present study did not find any significantly increased risks of induction of haematological malignancies compared with previous observations.

Table III. Patients with secondary haematological malignancy.

Date of initial diagnosis	Primary malignancy	Sex	Age, years	Oncological treatment and PGCSF used	Haematological malignancy	Date of subsequent diagnosis
January 2007	Germinal tumour (seminoma)	Male	63	Adjuvant CHT BEP 4x with 4x PF originator for FN primary prophylaxis in February-April 2007	Multiple myeloma	January 2022
January 2013	Breast cancer (HER2+)	Female	63	Adjuvant CHT 4x TAC with 3x PF originator for FN primary prophylaxis in September-November 2013 and adjuvant trastuzumab	Gastric diffuse large B-cell lymphoma	January 2020
June 2015	Triple negative breast cancer	Female	82	Adjuvant CHT 3x FEC + 3x docetaxel with 3x PF originator for FN primary prophylaxis in October-November 2015 and adjuvant RT	Multiple myeloma	September 2021
July 2015	Triple negative breast cancer, (germline mutation, <i>PALB2</i> c.3256C>T)	Female	51	Adjuvant CHT 6x TAC with 6x PF originator for FN primary prophylaxis in August-December 2015 and adjuvant RT	Follicular lymphoma	November 2022
March 2016	Ovarian cancer (HGS)	Female	70	Adjuvant CHT 5x PC with 1x PF originator and 1x LF for FN primary prophylaxis in June-August 2016 and palliative CHT 6x liposomal doxorubicin in September 2016- March 2017	Myelodysplastic syndrome with pancytopenia	August 2017
December 2016	Breast cancer	Female	70	Adjuvant CHT 6x AC with 2x PF originator for FN primary prophylaxis in July 2017 and adjuvant RT	Myelodysplastic syndrome; AML transformation	August 2019; February 2020
June 2017	Triple negative breast cancer	Female	83	Adjuvant CHT 6x CMF with 4x PF originator for FN primary prophylaxis in October-December 2017 and adjuvant RT	Multiple myeloma	June 2019

AC, doxorubicin + cyclophosphamide; AML, acute myeloid leukaemia; BEP, bleomycin + etoposide + cisplatin; CHT, chemotherapy; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; FN, febrile neutropenia; HGS, high grade serous; LF, lipegfilgrastim; PF, pegfilgrastim; PC, paclitaxel + carboplatin; *PALB2*, Partner And Localizer Of BRCA2; PGCSF, pegylated granulocyte colony-stimulating factor; RT, radiotherapy; TAC, docetaxel + doxorubicin + cyclophosphamide.

Regarding limitations, the retrospective design of this study raises the possibility of various biases. However, the single centre study with implemented standard electronic records of patients and PGCSF drugs administered can be considered a relatively reduced variability source of data. Additionally, the present study investigated a consecutive cohort of patients using primarily PGCSFs for the prophylaxis of FN or severe neutropenia. Accurately assessing the longer-term risks of LF and PF biosimilar compared with that of PF originator (which was related

to all cases of secondary haematological malignancies) requires longer follow-up. The incidence of secondary haematological malignancies in patients treated for solid tumours is a complex issue depending on several risk factors, particularly the type and duration of CHT. The most notable leukaemogenic effect was observed in alkylating agents, topoisomerase II inhibitors and particularly platinum compounds, all of which have been used for treatment purposes (23-25). Radiotherapy is also a known risk factor, wherein radiation dose was the main determinant of

secondary haematological malignancies (26). In breast cancer specifically, radiation alone has been reported to more than double the risk of both MDS and AML (27).

Individual genetic predispositions may also contribute to the development of a secondary haematological malignancy, given that the existence of several genetic syndromes and specific mutations, such as mutations in the FANCD1 or SBDS gene, are known to increase the risk of haematological malignancies, often through mechanisms involving bone marrow failure, such as Fanconi anaemia or Schwachman-Diamond syndrome (28,29). These syndromes are typically linked to mutations that affect DNA repair, ribosome biogenesis or telomere maintenance pathways, which compromise genomic stability and haematopoietic stem cell function. In the context of MDS specifically, it has been demonstrated that ~7% of patients carry a pathogenic germline mutation (30). However, in the present study cohort, routine germline genetic testing was not performed due to limited access to such testing in the past. Consequently, individuals with inherited predispositions could not be excluded. Notably, as aforementioned, within the present study cohort of patients with secondary haematological malignancies, one patient had been genetically tested (next-generation sequencing for germline mutations) and found to carry a pathogenic hereditary heterozygous gene mutation in *PALB2* (c.3256C>T). Mutations in the *PALB2* gene are reported to increase the risk not only of breast and pancreatic cancer, but also of lymphomas and leukaemias in both sexes (31). *PALB2* is a tumour suppressor gene that works as a crucial partner for the *BRCA2* protein, helping to localize it and facilitate its essential function in DNA double-strand break repair via homologous recombination (32). Therefore, there is a possibility that underlying hereditary factors may have contributed to the development of secondary haematological malignancies in a subset of patients in the present study.

In conclusion, the present retrospective study supported the previously established safety of PGCSFs for the treatment of patients with solid tumours. However, further observations with longer follow-up are recommended, particularly for LF and PF biosimilars, which have a relatively shorter safety follow-up compared with the PF originator.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SV organised the research, coordinated the gathering of scientific data and wrote the main manuscript. VK, JK, JD and TS collected data from the database. JF designed, supervised and organized the research, and reviewed the article. LM reviewed and expanded relevant data into the article. All authors read and approved the final manuscript. SV and LM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

According to the national ethical guidelines of the Czech Republic, no ethical approval was needed to conduct the present retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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