



Original research

Evidence-based AGIHO guideline update on prophylaxis of infectious complications with granulocyte-stimulating factors (G-CSF) for the treatment of adult patients with cancer

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ARTICLE INFO

Key words:

Granulocyte colony-stimulating factor
G-CSF
Erbemalenogastim alfa

ABSTRACT

Introduction: Febrile neutropenia, a common complication of systemic antineoplastic therapy, varies in risk depending on malignant disease, treatment, and patient factors. The risk increases with the depth and duration of neutropenia and can be reduced with prophylactic use of G-CSF. International guidelines are conflicting in several aspects and do not reflect all patient groups. We therefore updated the 2014 Infectious Diseases Working

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<https://doi.org/10.1016/j.ejca.2026.116244>

Received 23 December 2025; Accepted 31 December 2025

Available online 16 January 2026

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Cancer
Lymphoma
Acute leukemia
Biosimilar
Neutropenia
Infection
Febrile neutropenia
Supportive care

Party (AGIHO) guideline of the German Society of Hematology and Medical Oncology (DGHO) on evidence-based recommendations for the use of G-CSF in patients with cancer.

Materials and Methods: After a systematic literature search from January 2014 to December 2024 on PubMed and Medline several consensus meetings were held by an expert panel of the AGIHO to evaluate, discuss and consent on the level of evidence and strength of recommendation for the use of G-CSF in patients with cancer based on ESCMID criteria.

Results: Results from eligible (randomized) studies were grouped in evidence tables. Recommendations for different entities, risk groups, new G-CSF formulations and emerging strategies in immunotherapy were set up and put into comparison to 2014.

Discussion: Comprehensive literature search and expert panel consensus confirm most of the key recommendations of 2014. New recommendations on the use of G-CSF in immunotherapy settings provide insight and support for day-by-day clinical decision making in the care of patients with cancer.

1. Introduction

Febrile neutropenia (FN) is an important complication of cancer treatment. The risk depends on the underlying disease, the type and dosage of systemic therapy, and individual patient factors. The likelihood of developing FN increases with both the severity and duration of neutropenia. One possible strategy to reduce the risk of FN is the prophylactic (preventive) administration of G-CSF. In 2014, a comprehensive evidence-based guideline on prophylaxis of infectious complications with G-CSF in adult patients with cancer undergoing chemotherapy was published by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) [1]. The aim of that guideline was to provide evidence-based information for day-by-day clinical decision making in the care of adult patients with hematological and solid malignancies. Data analysis was focused on the effect of G-CSF on the prevention of fever, antibiotic use, dose intensity of chemotherapy, and overall survival (OS) regarding different disease entities. While antineoplastic treatment has substantially changed over the last decade, we provide here a comprehensive analysis of the published literature on the use and effects of G-CSF and related products since 2014, as well as an updated guideline on its use in immunotherapy.

2. Methods

Definition and classification of strength of a recommendation (SoR), as well as level (“quality”) of evidence (LoE) were based on European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria (Table 1) [2]. Following these criteria, our recommendations were developed and categorized by a panel of board-certified experts in internal medicine, hematology, medical oncology, infectious diseases, and intensive care using a stepwise consensus process. For this purpose, we performed a literature search in PubMed and Medline on G-CSF use

in patients with cancer published from 01/2014–12/2024, when the previous version of our guideline was published [1]. Available data were extracted, tabulated, and discussed by the guideline panel members in different meetings. Finally, the recommendations were approved by an AGIHO plenary meeting held in December 2024.

3. Short summary of 2014 recommendations

There was convincing evidence from numerous randomized trials (RCT) that G-CSF, biosimilar G-CSF, and pegfilgrastim reduce the risk of developing FN and infections. The relative benefit appeared to be highest for patients with an intermediate risk of infections [1]. The use of G-CSF may therefore reduce the need for hospitalization and antibiotic treatment, but a clear benefit for OS, tumor response (by increasing dose-intensity) or cost-effectiveness has not been shown.

4. What’s been new since 2014?

- **Hodgkin lymphoma:** BrECADD or BV+AVD are new standard immunochemotherapy protocols and should be complemented with the addition of G-CSF.
- **AML:** G-CSF is safe in the treatment of AML and should be considered regarding the shortening of neutropenia and duration of hospitalization.
- **Treatment with T cell engager products (CAR T, bispecific antibodies):** G-CSF administration in neutropenia after CAR T cell therapy and bispecific antibody treatment is safe. Incidence and duration of neutropenia as well as infections are reduced. However, no RCT data is available yet to date.
- **Biosimilar G-CSF** is at least non-inferior compared to originator G-CSF in terms of efficacy and survival and is a cost-effective alternative.
- **Efbemalenograstim alfa**, a third generation, long-acting non-pegylated G-CSF, is at least non-inferior compared to pegfilgrastim or filgrastim in terms of efficacy. Without the risk of inducing anti-PEG (polyethylene glycol) antibodies, it retains therapeutic efficacy with potentially fewer adverse effects.
- **To save antibiotics:** G-CSF for primary prophylaxis can help to save antibiotics.

5. G-CSF in the treatment of solid tumors

Since the landmark study from Crawford et al., 1991 [3], several clinical studies have been published addressing the reduction of infectious complications in solid tumors by using G-CSF. The conclusions are discussed in the prior version of this guideline [1]. G-CSF after chemotherapy reduces the incidence of FN but does not affect tumor response or survival [4]. The recent research focus on solid tumors has been on the safety and efficacy of biosimilars in this setting (as discussed in the section on biosimilar G-CSF below). Therefore, the recommendation for the use of G-CSF with chemotherapy in patients with solid tumors according to the expected risk for FN incidence is still valid (German S3

Table 1
Strength of a recommendation (SoR) and level (“quality”) of evidence (LoE) [2].

Grade (SoR)	A: AGIHO strongly supports a recommendation for useB: AGIHO moderately supports a recommendation for useC: AGIHO marginally supports a recommendation for useD: AGIHO supports a recommendation against use
Level (“quality”) (LoE)	I: Evidence from ≥ 1 properly designed RCT II*: Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments*Added indexr: Meta-analysis or systematic review of RCTs t: Transferred evidence, that is, results from different patients’ cohorts, or similar immune status h: Comparator group is a historical controlu: Uncontrolled trialaa: Published abstract (presented at an international symposium or meeting) III: Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Note. AGHIO, Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (DGHO); RCT, randomized controlled trial.

[5], ASCO [6] and ESMO guidelines [7]):

- Risk > 20 %: indication for G-CSF
- Risk < 10 %: no indication for G-CSF
- Risk 10–20 % and clinical risk factors: indication for G-CSF

6. G-CSF in the treatment of non-Hodgkin lymphoma

We evaluated six studies which were retrieved by a literature search with the keywords “G-CSF, lymphoma, randomized and clinical trial” (Table 2A). The AVOID study evaluated the efficacy of lipegfilgrastim vs. pegylated G-CSF (Peg-G-CSF) in the treatment of elderly patients with B-cell non-Hodgkin lymphomas (NHL) with rituximab plus CHOP (R-CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]) [8] and showed non-inferiority of lipegfilgrastim (A-I). Two RCT evaluated the effect of increased dose intensity using G-CSF [9,10]. R-CHOP-14 (every 14 days) plus G-CSF improved OS in comparison to R-CHOP-21 (every 21 days) in a study from Iran [10]. One other RCT evaluated the omission of G-CSF after autologous hematopoietic cell transplantation (HCT) for NHL or multiple myeloma (MM) [11]. No adverse effects on infectious complications or death by the omission of G-CSF were observed in this study population (B-I). One retrospective study analyzed whether primary respective secondary [12] use of G-CSF after immunochemotherapy may affect the treatment outcome and prognosis of patients with NHL. The secondary use of G-CSF resulted in more treatment delays in patients with NHL and chronic lymphocytic leukemia treated with rituximab and bendamustine [12]. A large retrospective study with a cohort of > 45,000 patients with lymphoma and solid tumors assessed the timing of the administration of G-CSF: Peg-G-CSF administered on the same day of chemotherapy resulted in a higher incidence of FN compared to the injection 2–4 days later [13].

In summary, no clear benefit of the use of G-CSF on OS in patients with B-NHL by increasing dose intensity has been shown to date (C-I). Secondary use of G-CSF resulted in more treatment delays compared to its primary use. It remains unclear whether the long-term outcome of these patients is affected by these treatment delays (C-II_u). The incidence of FN increases when G-CSF is administered on the day as chemotherapy; therefore, it is recommended to administer it on days 2–4 after completing cytotoxic treatment (B-II).

7. G-CSF in the treatment of Hodgkin lymphoma

7.1. With ABVD

Primary G-CSF prophylaxis is not routinely recommended in patients with Hodgkin lymphoma (HL) undergoing ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) treatment [14] but might be a clinically valid supportive option in selected patients with advanced age or

relevant comorbidities (C-II_u). However, it should be considered that G-CSF might increase the risk of bleomycin-induced lung toxicity [15]. Besides this, several studies showed that ABVD may be safely and effectively administered in full dose intensity without G-CSF support, regardless of the absolute neutrophil count (Table 2B) [16–18].

7.2. With AVD + brentuximab vedotin (BV) or nivolumab (N)

The phase III RCT ECHELON-1 compared BV+AVD (brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine) and ABVD as first-line therapy for classical HL (cHL) [19]. Neutropenia was evident in 58 % of the patients after BV+AVD and 45 % after ABVD. The rate of FN in patients receiving BV+AVD was lower among the 83 patients who received primary G-CSF prophylaxis than among those who did not (11 % vs. 21 %). Discussion with the independent data and safety monitoring committee led to the recommendation to use primary G-CSF prophylaxis in all patients attached to the BV+AVD arm.

A recently published phase II, open-label, multicenter study focused on stage I/II bulky and advanced-stage cHL. Patients of different age groups were evaluated for treatment with a combination of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine. G-CSF prophylaxis was optional per institutional guidelines. 49 % of patients received G-CSF, all for primary prophylaxis. Grade ≥ 3 treatment-related neutropenia occurred in 9 %, whereas no FN was observed [20] (B-II_u for elderly, C-II_u for younger patients).

A further phase III study evaluated brentuximab vedotin or nivolumab with AVD for advanced stage cHL (10 % >60 years of age). G-CSF prophylaxis was mandatory with BV+AVD but optional with N + AVD. G-CSF was administered in 97 % of patients with BV+AVD and 56 % with N + AVD. At least grade 3 neutropenia occurred in 48 % vs. 26 % of patients after N + AVD and BV+AVD, respectively. Rates of neutropenia, sepsis, or infections were similar between both arms [21].

In summary, the guideline group recommends primary G-CSF prophylaxis for both younger (B-II_u) and elderly patients (A-II_u) receiving BV+AVD as first-line treatment for advanced (stage III/IV) HL (Table 2B).

7.3. With BEACOPP/BrECADD

Prophylactic G-CSF should be given in all patients with HL undergoing escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) or BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) therapy (A-II_u) since it was mandatory for both regimens in the study protocol (in pegylated or non-pegylated form as per investigator's discretion) (Table 2B) [22–24].

Table 2A
Recommendations for G-CSF in the treatment of non-Hodgkin lymphoma.

Population/clinical situation	Intention	Intervention	SoR/LoE	References	Comments
Aggressive NHL	To obtain dose intensity	CEOP vs. high CEOP + G-CSF	D-I	[9]	Pre-rituximab
Indolent and aggressive B-NHL	To obtain dose intensity	R-CHOP-14 + G-CSF vs. R-CHOP-21	C-I	[10]	Improved survival with R-CHOP-14 in opposite to previous publications
B-NHL	To assess non-inferiority of lipegfilgrastim vs. peg G-CSF	R-CHOP 21 + peg vs. lipegfilgrastim	A-I	[8]	Lipegfilgrastim non inferior
NHL, multiple myeloma after autologous HCT	To assess whether omission of G-CSF after SCT affects efficacy or toxicity	Randomization: G-CSF or not after HCT	B-I	[11]	Infectious complications or death not affected by the omission of G-CSF
R-bendamustine in CLL and NHL	To assess outcome with primary vs. secondary G-CSF	G-CSF given primary or secondary	C-II _u	[12]	Secondary application results in more dose delays
NHL and solid tumor (n = 45,592)	To assess whether timing of peg-G-CSF application affects febrile neutropenia	G-CSF on d1 vs. d 2–4	B-II _u	[13]	More FN when G-CSF administered on day 1

Note. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; LoE, level of evidence; SoR, strength of recommendation. SCT stem cell transplantation. R Rituximab

Table 2B

Recommendations for G-CSF in the treatment of Hodgkin lymphoma.

Population/clinical situation	Intention	Inter-vention	SoR/LoE	References	Comments
Patients with Hodgkin lymphoma treated with ABVD 1st line	To reduce incidence of grade 3 neutropenia and FN	Primary or secondary G-CSF prophylaxis	C-II _u (G-CSF prophylaxis is not routinely recommended)	[14]	G-CSF prophylaxis must be critically weighted since it might increase the risk of lung fibrosis under bleomycin [15]; ABVD may be safely and effectively administered in full dose intensity without G-CSF support, regardless of the ANC [16–18]
Patients with cHL, 1st line BVN+AD or N + AVD (different age groups)	To reduce incidence of grade 3 neutropenia and FN	Primary G-CSF prophylaxis	B-II _u (might be primary used for elderly patients), for younger patients C-II _u	[20,21]	
Patients with cHL treated with BV+AVD 1st line	To reduce incidence of grade 3 neutropenia and FN	Primary G-CSF prophylaxis	A-II _u (elderly patients and those with comorbidities), B-II _u (younger patients without comorbidities)	[19,21,86, 87]	
Patients with HL treated with eBEACOPP, and patients with cHL treated with BrECADD 1st line	To reduce incidence of grade 3 neutropenia and FN	Primary G-CSF prophylaxis	A-II _u	[22–24]	Mandatory in the study protocols

Note. BV+AVD, brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine; ABVD doxorubicin, bleomycin, vinblastine and dacarbazine; AD, doxorubicin and dacarbazine; BVN + AD, brentuximab vedotin plus nivolumab, + doxorubicin and dacarbazine; BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; N + AVD, nivolumab with doxorubicin, vinblastine, and dacarbazine; ANC absolute neutrophil count; SoR, strength of recommendation; LoE, level of evidence

8. G-CSF in the treatment of acute leukemia

8.1. Acute myeloid leukemia

In patients with acute myeloid leukemia (AML), myeloid growth factors have been used in studies both for „priming“, with the aim of achieving a more effective cytostatic effect, and prophylaxis against infections. Priming is not the subject of this guideline. Regarding infection prophylaxis, the data from several RCTs published until the end of 2013 did not show any benefit of prophylactic administration of growth factors after intensive induction or consolidation for the primary endpoints of OS or prevention of proven infections, so that no clear recommendation for the administration of growth factors was given in our 2014 guideline. Corresponding results are also summarized in two meta-analyses, largely evaluating the same studies [25,26]. In subsequent sub-analyses of these trials, however, it was shown that G-CSF prophylaxis had a positive effect in terms of reducing neutropenia, the duration of hospitalization, and the duration of antibiotic treatment but not on OS (Table 3). No new safety signals appeared [25,26] (B-I). A more recent study could reproduce the significant reduction of neutropenia duration after cytarabine consolidation using pegfilgrastim in an intra-patient comparison in a cohort > 60 years of age [27] (B-II_u). For patients undergoing medium-intensity consolidation with high-dose cytarabine (≥60 years) G-CSF shows effects on the reduction of neutropenia comparable to the meta-analyses mentioned above and in addition, also a benefit regarding infections [28] (B-II_u). In view of the

favorable side effect profile and the significant reduction in costs of growth factors in the last few years, aspects such as shorter hospital stays and shorter antibiotic treatment should be considered. One possible disadvantage of G-CSF use after AML induction therapy is a more difficult assessment of early blast clearance, e.g., at day 14. Thus, G-CSF was not allowed before day 14, if blast clearance was to be assessed in clinical trials (e.g., DaunoDouble; [29]) and a similarly restrictive use is also recommended outside clinical trials for patients with intended analysis of early blast clearance.

Overall, it is sufficiently well established that a shortening of neutropenia can be regularly achieved with G-CSF. In addition to this effect, it seems plausible that a clinical benefit in terms of avoiding infectious episodes can be achieved in situations, in which cytostatic treatment is not maximally intensive, such as consolidation with high-dose cytarabine on three consecutive days, where infectious episodes were described in combination with G-CSF in only around one third of cycles [28] (B-II_u).

8.2. Acute lymphoblastic leukemia

The administration of G-CSF was already recommended in the previous version of this guideline based on existing comparative studies that showed a reduction in infections. In a 2017 meta-analysis based on seven RCTs, a benefit was also described for OS [30]. In Germany, acute lymphoblastic leukemia (ALL) is mainly treated in accordance with the GMALL study group recommendations. Here, the routine use of growth

Table 3

Recommendations on G-CSF use for acute leukemia.

Population	Intention	Intervention	SoR/LoE	References	Comments
AML (induction and consolidation)	To shorten neutropenia and duration of hospitalization	G-CSF (GM-CSF) vs. none	B-I	[25,26]	Meta-analysis (GM-CSF included in [26])
AML consolidation	To prevent febrile neutropenia	Pegfilgrastim vs. none	B-II _u	[27,28]	No randomized trials
AML (induction and consolidation)	To reduce mortality	G-CSF (GM-CSF) vs. none	C-I	[25,26]	Meta-analysis (GM-CSF included in [26])
AML (induction and consolidation)	To assess equivalence of standard G-CSF and preparations with extended activity	G-CSF vs. pegfilgrastim	A-I	[88]	Randomized phase II trial
ALL induction	To reduce duration of neutropenia, severe infections and mortality	G-CSF vs. none	A-IIr	[30]	Meta-analysis of small trials

Note. G-CSF, granulocyte-colony stimulating factor; LoE, level of evidence; SoR, strength of recommendation.

factors is recommended; the feasibility of the same therapy without growth factors has not been established. The use of long-acting G-CSF can be used in cyclical therapies, that are primarily used in consolidation, in analogy to other cyclical therapies. During frequent repetitive chemotherapy administration (e.g., induction following GMALL recommendations), conventional G-CSF is recommended (Table 3).

9. Secondary application of G-CSF

The concept of secondary application of G-CSF is used in two different scenarios: (i) application of G-CSF to maintain dose intensity in a curative setting by speeding granulocyte recovery; or (ii) to reduce the incidence of FN + /-other infectious complications in the following cycles after FN in the previous chemotherapy cycle. There are very few RCT addressing these questions. Regarding dose intensity, e.g., in breast cancer patients [31], the administration of G-CSF results in a higher dose intensity in patients with breast cancer improving outcome. Regarding mortality: there is no proof for any regimen to date that secondary G-CSF intervention in FN reduces mortality. Regarding morbidity, our recommendation to use G-CSF in these clinical settings is in line with the German S3 [5], ASCO [6] and ESMO guidelines [7]: it is recommended after a neutropenic complication in the previous cycle has occurred (B-III).

10. G-CSF after CAR T cell therapy

Immunotherapy approaches have rapidly evolved in the last years after the introduction of new cellular therapeutic options such as genetically engineered chimeric antigen receptor (CAR) T cell therapy as well as off-the shelf approaches applying bispecific antibodies. Immune effector cell-associated hematotoxicity (ICAH; classified early vs. late) is a common adverse event for CAR T cell therapy [32–34] predisposing for clinically relevant infections [35]. The underlying pathophysiological mechanisms of ICAHT are still poorly understood, translational studies point to a multifactorial event, e.g., CAR T cell-driven inflammation causing prolonged pancytopenia by a cytokine-mediated stem cell quiescence [36]. G-CSF support is recommended by current reviews [36] suggesting that the CAR-HEMATOTOX risk model [37,38] may guide the use of G-CSF. Of note, G-CSF application was so far not associated with an increase in $\geq$ grade 3 cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) [39–41]. If patients are refractory to G-CSF support and neutropenia is life-threatening and/or prolonged ($<20\%$ of patients), hematopoietic cell boost may be an option [42,43]. To date, the optimal time point for the application of G-CSF in this scenario has not been defined. Pegylated or non-pegylated formulations can be used with the same therapeutic effect. Retrospective studies support safety when using G-CSF [44].

In summary, we recommend the use of G-CSF in neutropenia after CAR-T cell treatment. However, due to a lack of RCTs, the strength of recommendation and Quality of Evidence is based on retrospective data and expert opinion (B-III).

11. G-CSF after treatment with bispecific antibodies (BsAb)

There are large differences in the risk of neutropenia and FN between the BsAb for hematologic neoplasms and solid tumors [45]. For example, the rate of neutropenia was 12 % and for FN 0.5 % with tarlatamab for small cell lung cancer. For non-small cell lung cancer and amivantamab combined with carboplatin/pemetrexed chemotherapy, the incidence of FN was 3 %, and $\geq$ grade 3 neutropenia occurred in 33 % of patients [46].

The rate of grade 3–4 neutropenia in the treatment of B-cell precursor ALL with blinatumomab was 45 % [47], with epcoritamab in diffuse large cell lymphoma (DLBCL) 10.8 % [48], in follicular lymphoma, 26 % [49] with glofitamab in DLBCL with monotherapy, 27 % [50], and 30 % with combination chemotherapy with G-CSF prophylaxis

[51]. With mosunetuzumab, the rate of neutropenia in DLBCL was 25 % [52], in combination with polatuzumab vedotin 25 % [53], and 19 % in odronextamab therapy of B-cell malignancies [54].

Thus, in patients with treatment related neutropenia, the use of G-CSF may be considered [55]. It should be noted that BsAb therapy can be discontinued in accordance with the approval and that the patient's disease control must be weighed against the risk of neutropenia (B-III). BsAb therapy may be continued if lymphoma causing cytopenia due to bone marrow infiltration or organomegaly is suspected (B-III). In MM, treatment with BsAb frequently results in profound neutropenia [56], with an incidence of grade 3 neutropenia of 22.1–64.2 %. Guidelines for the use of G-CSF exist and have been published by the International Myeloma Working Group immunotherapy committee [56]. Our group recommends adherence to this guideline. G-CSF should not be administered during step-up dosing or during CRS (B-III). It should also be avoided when a patient is at risk for CRS [57] and the symptoms of FN and CRS overlap [58]. Prospective RCT regarding the use of G-CSF during BsAb treatment are warranted.

12. Biosimilar G-CSF and efbemalenograstim alfa

In general, biosimilar trials are designed to show therapeutic equivalence, but not superiority [59,60]. However, in our view, therapeutic non-inferiority is sufficient for transfer of the concept into clinical routine [61] corresponding to 'strongly' support a recommendation for use (SoR grade A; Table 1).

There is clear evidence for patients with solid tumors, mostly breast cancer, that biosimilar G-CSF is at least non-inferior compared to originator G-CSF in reducing the FN rate after chemotherapy [62–66] (Table 4) (A-I). For patients with breast cancer receiving biosimilar pegfilgrastim or originator filgrastim there were numerical differences in FN rates, but these differences were not significant for cycle 1 (difference, 2.4; $p = 0.35$) or for 6 cycles (difference, 4.0; $p = 0.18$) [65]. These results were confirmed in another study investigating biosimilar pegfilgrastim and originator pegfilgrastim in patients with breast cancer (3.4 % vs. 1.7 %; $p = 0.56$) [66]. For hematological malignancies, both biosimilar pegfilgrastim and filgrastim showed no difference compared to originator pegfilgrastim and filgrastim in reducing FN [67–69] (Table 4) (A-II_h). A multicenter study on 626 patients with MM or NHL receiving autologous HCT showed no difference in the rate of FN for biosimilar compared to originator pegfilgrastim (75 % vs. 81 %; $p = 1.00$) [70]. The same was true for patients treated with biosimilar filgrastim or originator filgrastim after induction/consolidation chemotherapies or autologous/allogeneic HCT (47.3 % vs. 55.4 %; $p = 0.32$) [69].

Many studies including phase III RCTs [63–66,71,72] showed at least non-inferiority for biosimilar compared to originator G-CSF shortening neutropenia after chemotherapy (Table 4) (A-I). A pooled study of 2 phase III RCTs on patients with breast cancer ($n = 624$) [62] showed no difference for duration of severe neutropenia or time to neutrophil recovery using biosimilar pegfilgrastim vs. originator pegfilgrastim, or biosimilar filgrastim vs. originator filgrastim. Using biosimilar pegfilgrastim or biosimilar filgrastim in patients with MM receiving autologous HCT, the time to neutrophil recovery (10 and 11 days, respectively) was the same as for originator filgrastim (10 days) [68]. A matched cohort study on patients with hematologic malignancies who received induction/consolidation chemotherapy or HCT also found no difference in the time to neutrophil recovery after therapy using biosimilar or originator filgrastim (mean 10.3 vs. 10.5 days; $p = 0.58$) [69] (Table 4) (A-II_h).

Using biosimilar G-CSF, the depth of neutropenia (grade 3–4) is reduced in the same way as using originator G-CSF, as shown by several studies [62,63,65]. A pooled analysis of 2 phase III RCTs with 624 patients with breast cancer showed no difference in the infection rate in the first chemotherapy cycle with biosimilar pegfilgrastim compared to pegfilgrastim (5.4 % vs. 5.8 %) [62]. A retrospective, multicenter study

Table 4

Recommendations for biosimilar G-CSF and efbemalenograstim alpha.

Population/clinical situation	Intention	Intervention	SoR/LoE	References	Comments
Breast/solid cancer	To reduce FN	BIO-pegfilgrastim, BIO-filgrastim	A-I	[62–67,71, 89–91]	BIO-pegfilgrastim, BIO-filgrastim vs. pegfilgrastim, filgrastim; non-inferiority/equivalence
Hematological cancer	To reduce FN	BIO-pegfilgrastim, BIO-filgrastim	A-II _h	[67–69,89,90]	BIO-pegfilgrastim, BIO-filgrastim vs. pegfilgrastim, filgrastim; no difference
Breast cancer	To shorten neutropenia	BIO-pegfilgrastim, BIO-filgrastim	A-I	[62–66,72,92]	BIO-pegfilgrastim, BIO-filgrastim vs. pegfilgrastim, filgrastim; non-inferiority/equivalence
Hematological cancer	To shorten neutropenia	BIO-pegfilgrastim, BIO-filgrastim	A-II _h	[68,69]	BIO-pegfilgrastim, BIO-filgrastim vs. pegfilgrastim; no difference
Breast cancer	To reduce depth of neutropenia	BIO-pegfilgrastim, BIO-filgrastim	A-I	[62,63,65,71, 92]	BIO-pegfilgrastim, BIO-filgrastim vs. pegfilgrastim, filgrastim; non-inferiority/equivalence
Hematological and solid cancer	To prevent documented infection	BIO-pegfilgrastim, BIO-filgrastim	A-I	[70]	BIO-pegfilgrastim, BIO-filgrastim vs. Pegfilgrastim, filgrastim; non-inferiority/equivalence
Breast cancer	To reduce infection-related mortality	BIO-pegfilgrastim	A-I	[66]	BIO-pegfilgrastim vs. pegfilgrastim; non-inferiority/equivalence
Hematological and solid cancer	To reduce financial costs/to improve cost-effectiveness	BIO-pegfilgrastim, BIO-filgrastim	A-II _h	[69,70,75,76, 93,94]	Mostly simulation modeling, mostly USA; cost saving BIO-pegfilgrastim, BIO-filgrastim > pegfilgrastim, filgrastim
Breast cancer	To shorten neutropeniaTo reduce depth of neutropenia To reduce FN	EMGA	A-I	[80–83]	EMGA vs. pegfilgrastim, filgrastim, placebo; non-inferiority
		EMGA	A-I	[81,82]	EMGA vs. pegfilgrastim, placebo; non-inferiority
		EMGA	A-I	[81–83]	EMGA vs. pegfilgrastim, filgrastim, placebo; non-inferiority

Note. BIO, biosimilar; EMGA, efbemalenograstim alfa (benegrastim); FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; LoE, level of evidence; SoR, strength of recommendation.

on patients with non-myeloid cancers ($n = 3542$) found no difference in the combination of neutropenia and infection in cycle 1 between biosimilar filgrastim and filgrastim (2.3 % vs. 1.7 %) [67]. A matched-pair analysis of 626 patients with autologous HCT for lymphoma and MM revealed no difference regarding microbiologically defined infections in the subgroup of patients with lymphoma (44 % vs. 37 %; $p = 0.72$) or with MM (45 % vs. 36 %; $p = 0.54$) for patients treated with biosimilar pegfilgrastim and filgrastim, respectively, post HCT [70].

Regarding infection-related mortality, studies on patients with breast cancer found no clinically meaningful differences between biosimilar G-CSF-treated patients and those treated with originator G-CSF [62,66] (A-I). No difference in OS was found for patients with hematological malignancies and solid tumors who received biosimilar G-CSF or originator G-CSF [73,74] (Table 4)(A-II_h).

Many studies showed that biosimilar G-CSF was cost-effective for patients with solid tumors as well as hematological malignancies. However, most data exist for simulation modeling studies [75,76]. In addition, real-world comparison data are also available. A retrospective, observational, matched cohort study on 148 patients with hematological malignancies, including those received HCT, showed a significant cost reduction for biosimilar filgrastim compared to filgrastim (for all patients, US\$ 77,560 vs. 228,010; $p < 0.001$) [69]. A multicenter study from Italy with 626 patients with lymphoma and MM who received autologous HCT showed that biosimilar pegfilgrastim was cost-effective when compared with the other G-CSF (average total costs per patient € 18,219 vs. 19,755–23,708) [70]. Therefore, in terms of reducing financial costs or improving cost-effectiveness, it is highly recommended to use biosimilar instead of conventional G-CSF (Table 4) (A-II_h).

Taken together, using biosimilar G-CSF for prophylaxis of infections in patients with cancer is recommended (Table 4) (A-I).

Efbemalenograstim alfa (EMGA; benegrastim), is a non-biosimilar third generation, long-acting recombinant fusion protein containing G-CSF and a human IgG2-Fc fragment [77]. Pegylation (conjugating PEG) of G-CSF is successful in decreasing renal clearance and therefore prolonging its half-life, but many patients acquire anti-PEG antibodies due to PEG exposure from various products (laxatives, cosmetics) [78]. Anti-PEG antibodies are associated with decreased therapeutic efficacy and an increase in adverse effects [79]. EMGA – non-pegylated – has the potential to be a substitute for pegfilgrastim. So far, EMGA has been investigated primarily in patients with breast cancer. In multicentre

phase II-III RCTs with up to 393 patients, EMGA was at least non-inferior compared to pegfilgrastim/filgrastim and placebo. Compared to pegfilgrastim [80,81] or to filgrastim [82], EMGA was non-inferior in shortening the time with severe neutropenia; however, compared to placebo, EMGA significantly reduced the time with grade 4 neutropenia in the first cycle from a mean of 3.9–1.3 days ($p < 0.001$) [83]. Furthermore, the rate of FN in cycle 1 was lower in the EMGA than in the placebo group (4.8 % vs. 25.6 %; $p < 0.002$) [83].

Therefore, EMGA is an alternative compared to pegfilgrastim and/or filgrastim (Table 4) (A-I).

13. G-CSF as part of antibiotic stewardship programs

In a RCT, patients with breast cancer ($n = 458$) receiving G-CSF for primary prophylaxis were less likely to experience FN (5.7 % vs. 15.8 %; $p < 0.001$) than patients receiving ciprofloxacin [84]. This suggests lower antibiotic consumption. In a placebo-controlled RCT, the addition of G-CSF to patients with breast cancer undergoing myelosuppressive chemotherapy reduced the rate of antibiotic therapy (10.8 % vs. 33.3 %; $p = 0.005$); this allowed nearly one in five patients to avoid antibiotics altogether [83]. Another RCT showed that primary G-CSF prophylaxis after high-dose chemotherapy and autologous HCT in patients with MM or lymphoma can reduce antibiotic consumption (median treatment duration 4 vs. 7 days; $p = 0.001$) [11]. A large study ($n = 3163$) that included patients with solid tumors and aggressive NHL showed that the number needed to treat with G-CSF for primary prophylaxis to prevent one FN episode was almost half that of patients receiving antibiotics prophylaxis [85].

Therefore, as one component of Antibiotic Stewardship, G-CSF can help to save antibiotics. G-CSF should be preferred over antibiotics whenever reasonable for primary prophylaxis of FN/infections due to putative long term detrimental effects of antibiotics (A-I).

14. Summary of the guideline recommendations

Supportive care with G-CSF is well established in the treatment of patients with cancer. As immunotherapy strategies emerge in the treatment of hematological malignancies resulting in profound cytopenia, recommendations on the use of G-CSF as an intervention for neutrophil recovery and infection prophylaxis are comprehensively

covered in this guideline.

Accordingly, it confirms the previous recommendations from 2014 regarding chemotherapy-associated neutropenia. G-CSF should be used in clinical practice according to study group recommendations (e.g., ALL, Hodgkin lymphoma) when RCTs are missing. In the emerging field of immunotherapies (especially BsAb and CAR T cell therapies) RCTs are warranted to ensure optimal side effect management of CRS, ICANS and infections under G-CSF. Furthermore, biosimilar G-CSF is a cost-effective alternative compared to originator G-CSF, and at least non-inferior in many clinically relevant endpoints. Without the potential to cause anti-PEG antibodies, efbemalenograstim alfa is at least non-inferior compared to pegfilgrastim/filgrastim in terms of efficacy.

Author contributions

All authors were involved in the stepwise consensus process, including literature review, data extraction and tabulation, panel discussion, and revised and approval of the final manuscript version. MS, ES and RSB developed the first draft version of the manuscript. NS and MS wrote the chapter on solid tumors, MSH and LK the chapter on Hodgkin lymphoma, MS, ES and WN the chapter on NHL, SK and SM the chapter on acute leukemia, RSB and HL the chapter on T-cell engager therapies, RSB and ES the chapter on biosimilar G-CSF and EMGA, RSB and WH the chapter on secondary application of G-CSF. The final draft was consented by all other authors.

CRedit authorship contribution statement

Mellinghoff Sibylle: Validation, Writing – original draft, Writing – review & editing. **Krause Stefan:** Validation, Writing – original draft, Writing – review & editing. **Hartmut Link:** Validation, Writing – original draft, Writing – review & editing. **Philipp Köhler:** Validation, Writing – review & editing. **Nikolai Schuelper:** Validation, Writing – original draft, Writing – review & editing. **Martin Schmidt-Hieber:** Validation, Writing – original draft, Writing – review & editing. **Blasius Liss:** Validation, Writing – review & editing. **Enrico Schalk:** Validation, Writing – original draft, Writing – review & editing, Conceptualization. **Heinz Werner:** Validation, Writing – original draft, Writing – review & editing. **Rosanne Sprute:** Validation, Writing – review & editing. **Karsten Spiekermann:** Validation, Writing – review & editing. **Lea Kausche:** Validation, Writing – original draft, Writing – review & editing. **Ruth Seggewiss-Bernhardt:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Michael Sandherr:** Conceptualization, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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