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Annals of Oncology 25: 1709–1718, 2014
doi:10.1093/annonc/mdu035
Published online 14 March 2014

Prophylaxis of infectious complications with colony-stimulating factors in adult cancer patients undergoing chemotherapy – evidence-based guidelines from the Infectious Diseases Working Party AGIHO of the German Society for Haematology and Medical Oncology (DGHO)

J. J. Vehreschild¹, A. Böhme², O. A. Cornely^{1,3,4*}, C. Kahl⁵, M. Karthaus⁶, K.-A. Kreuzer¹, G. Maschmeyer⁷, S. Mousset⁸, V. Ossendorf³, O. Penack⁹, M. J. G. T. Vehreschild¹ & J. Bohlius¹⁰

¹1st Department of Internal Medicine, University Hospital of Cologne, Cologne; ²Onkologikum Frankfurt am Museumsufer, Frankfurt a.M.; ³Clinical Trials Centre Cologne (ZKS Köln, BMBF 01KN1106); ⁴Centre for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne; ⁵Clinic for Haematology and Oncology, Klinikum Magdeburg gGmbH, Magdeburg; ⁶Haematology-Oncology and Palliative Care, Hospital Neuperlach and Hospital Harlaching, Munich; ⁷Department of Haematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann, Potsdam; ⁸Medizinische Klinik II, University Hospital Frankfurt a.M., Frankfurt a.M.; ⁹Campus Benjamin Franklin; Medical Clinic for Haematology and Oncology, University Hospital Charité, Berlin, Germany; ¹⁰Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland

Received 13 April 2012; revised 18 December 2013; accepted 31 December 2013

Background: Current evidence on myelopoietic growth factors is difficult to overview for the practicing haematologist/ oncologist. International guidelines are sometimes conflicting, exclude certain patient groups, or cannot directly be applied to the German health system. This guideline by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO) gives evidence-based recommendations for the use of G-CSF, pegylated G-CSF, and biosimilars to prevent infectious complications in cancer patients undergoing chemotherapy, including those with haematological malignancies.

Methods: We systematically searched and evaluated current evidence. An expert panel discussed the results and recommendations. We then compared our recommendations to current international guidelines.

Results: We summarised the data from eligible studies in evidence tables, developed recommendations for different entities and risk groups.

Conclusion: Comprehensive literature search and expert panel consensus confirmed many key recommendations given by international guidelines. Evidence for growth factors during acute myeloid leukaemia induction chemotherapy and pegfilgrastim use in haematological malignancies was rated lower compared with other guidelines.

Key words: cancer, evidence-based guideline, febrile neutropenia, G-CSF, infection, supportive care

*Correspondence to: Prof. Oliver Cornely, Uniklinik Köln, Klinik I für Innere Medizin, Herderstr. 52-54, 50931 Köln, Germany. Tel: +49-221-478-6494; Fax: +49-221-478-3611; E-mail: oliver.cornely@uk-koeln.de

introduction

Myelosuppression due to cytotoxic drugs is a major limiting factor in the treatment of malignant diseases. Neutropenia places patients at a high risk of fever, infections, sepsis, and ultimately death [1, 2]. These risks are typically encountered with a graduated approach of anti-infective prophylaxis, myelopoietic growth factors, early empiric anti-infective treatment, and standardised diagnostic algorithms. As infection-related mortality is typically low during short-term neutropenia, studies in the field use end points more easily observed but with clinical relevance, such as febrile neutropenia (FN) or diagnosed infection. Apart from higher hospitalisation and mortality [3–5], FN and neutropenia-related infections may result in dose-reduction of cytotoxic drugs or longer intervals between treatment courses [6].

G-CSF was licensed in 1991 by the United States Food and Drug Administration (FDA) for use in patients undergoing cytotoxic treatment. Like all CSFs available today, it is administered subcutaneously and was approved for decreasing the incidence of FN and reducing the duration of neutropenia and fever following myeloablative chemotherapy [7]. Two different G-CSF preparations are available: non-glycosylated G-CSF filgrastim (Neupogen®; Amgen, Thousand Oaks, CA) and glycosylated G-CSF lenograstim (Granocyte®; Chugai, Utsunomiya, Japan). While data from two open-label randomised studies comparing filgrastim to lenograstim are conflicting [8, 9], and preclinical trials have demonstrated differences between both drugs pharmacokinetics and pharmacodynamics [10], and a recent systematic review demonstrated comparable efficacy of both drug [11].

The addition of a polyethylene glycol (PEG) molecule to filgrastim increases the serum half-life of filgrastim and allows reducing the frequency of G-CSF applications from a once daily to a once per chemotherapy cycle/three weekly schedule [12]. Pegfilgrastim is approved to decrease incidence of fever and infections in patients with non-myeloid malignancies and acute leukaemia receiving chemotherapy. Pre-clinical and clinical studies suggest that pegfilgrastim and filgrastim have comparable biologic activity and safety profiles [13, 14] as well as clinical efficacy [15–20].

More recently, biosimilar G-CSF (XM02) has been developed [21–23] and is also named with the non-proprietary name filgrastim. Further biosimilars have become available on the market.

Today, the American Society of Clinical Oncology (ASCO), the American National Comprehensive Cancer Network (NCCN), and the European Organisation for Research and Treatment of

Cancer (EORTC) have set-up guidelines for the use of G-CSF and GM-CSF in patients receiving chemotherapy with the objective to prevent fever and infections and to maintain chemotherapy dose intensity [24–27]. Following two landmark trials showing a significant reduction of FN by G-CSF administration even in intermediate- and low-risk patients [28, 29], the ASCO, NCCN, and EORTC [21, 30–32] updated their guidelines and now advocate the use of colony-stimulating factors to prevent FN in patients at a >20% risk for fever [30–34]. Risk factors can be used to identify patients with a particularly high risk to develop FN in ambiguous cases. Recently, validated risk factors for FN include prior chemotherapy, abnormal hepatic and renal function, low white blood count, chemotherapy, and planned delivery of $\geq 85\%$ of the dose of chemotherapy [35]. A comparison of international guideline recommendations is provided in Table 1.

The aim of this guideline is to identify and assess the evidence for the effects of G-CSF, pegfilgrastim, and biosimilar XM02 to assist in evidence-based clinical decisions on the primary and secondary prevention of infections in adult patients with haematological malignancies or solid tumours undergoing chemotherapy.

methods

We provide a detailed description of the methodology used for this guideline in the guideline report (supplementary File 01, available at *Annals of Oncology* online). In brief, we conducted a systematic literature search for trials using G-CSF, GM-CSF, pegylated filgrastim, or biosimilar filgrastim as prophylaxis of FN or infection during standard chemotherapy regimens in adult patients with solid tumours or haematological malignancies. For the search, we used a predefined search strategy, which is also part of the guideline report (supplementary File 01, available at *Annals of Oncology* online). We conducted all literature searches for the period January 1990 to August 2013.

Data were extracted by one reviewer and checked for accuracy by a second. Studies were categorised into three different groups of myelosuppression based on the risk of FN in the control arm: low risk: 0%–20%, moderate risk: 20%–40%, and intensive therapies with high risk >40% for FN. These cut-offs were chosen to reflect the development and changes of the guidelines provided by ASCO [26, 27] and NCCN [30]. Two recent guidelines used a wider definition for ‘high-risk’ patients (>20% risk for FN)

Table 1. Comparison of international guideline recommendations

Neutropenic event risk	ASCO 2000 [26]	ASCO 2006 [27]	EORTC 2010 [32]	NCCN 2012 [34]	AGIHO 2013
High risk	Use CSF $\geq 40\%$	Use CSF $\geq 20\%$	Use CSF $\geq 20\%$	Use CSF $\geq 20\%$	Use CSF $\geq 40\%$
Moderate to high	CSF not recommended				Use CSF $\geq 20\%$
Intermediate	Not further specified	Recommend <20% with risk factors	Consider CSF 10–20% with risk factors	Consider CSF 10–20% with risk factors	Recommend <20% with risk factors
Low	Not further specified	Not further specified	CSF is not recommended <10%	CSF is not recommended for most patients <10%	Not further specified

[32, 34]; however, it was decided to stay with the pre-defined definition used in our analysis.

An expert panel of the AGIHO reviewed all evidence tables and ranked the quality of evidence and strength of recommendation separately for different groups of diseases and FN risk categories (see guideline report for details). Levels of evidence were ranked based on the classification of the Infectious Disease Society of America [36]. With this guidance, the team of authors drafted a manuscript with evidence-based recommendations and presented this document to the panel for further discussion.

All included studies are listed in the evidence tables in supplementary File 02, available at *Annals of Oncology* online. In these evidence tables, studies are listed in the following order: disease entity, CSF used, placebo-controlled study, size of study. If

sufficient data were reported, studies with elderly patients are presented in separate tables. A list of chemotherapeutic regimens and the associated risk of FN were not part of the consensus process. Such lists are available as part of other guidelines [27, 32, 34].

Recommendations have been summarised in Tables 2 and 3.

use of G-CSF for primary prevention of infections

solid tumours

In 12 RCTs, G-CSF was used as primary prophylaxis in patients with solid tumours undergoing myelosuppressive chemotherapy [21, 28, 37–43, 78–84]. One study reported only infection rates

Table 2. Use of colony stimulating factors to prevent febrile neutropenia after myelosuppressive chemotherapy

Setting	Expected fever incidence during neutropenia	SoR	QoE	References	Comment
G-CSF					
Adult patients with solid tumours (e.g. SCLC, sarcoma)	≥20%	A	I	[28, 37–41]	
Adult patients with breast cancer, colorectal cancer, or ovarian cancer	<20%	B	I	[42, 43]	Since the clinical benefit is relatively small, we do not recommend routine use of G-CSF in these circumstances.
Adult and elderly patients with HL/NHL	≥40%	A	I/III ^a	[44–47]	QoE is I for NHL and III for HL.
Adult and elderly patients with HL/NHL	≥20%, <40%	B	II/III ^a	[48, 49]	QoE is II for NHL and III for HL.
Adult patients with myelodysplastic syndrome undergoing palliative chemotherapy	≥20%	D	II	[50, 51]	
Adult patients with ALL undergoing induction or consolidation treatment	≥40%	A	II	[52–54]	
Adult patients with ALL undergoing maintenance treatment	Any	C	III		No data
Adult patients with AML undergoing induction or consolidation chemotherapy	≥40%	C	I/II	[55–61]	Good evidence against a benefit, not generally recommended. QoE is I for induction and II for consolidation chemotherapy.
Elderly patients with AML undergoing induction chemotherapy	≥40%	C	I	[62–69]	Good evidence against a benefit, not generally recommended.
Other tumours and/or other risk categories	Any	B	III	[35]	Decision for G-CSF depending on individual patient risk factors
Pegfilgrastim					
Adult patients with solid tumours (e.g. breast cancer)	≥20%	A	I	[15–17, 29, 70]	Non-inferior to G-CSF
Adult patients with malignant lymphoma	≥20%	B	II	[18–20]	No studies testing for non-inferiority
Other tumours and/or other risk categories	Any	B	III	[35]	Decision for pegfilgrastim depending on individual patient risk factors
XM02					
Adult patients with NHL, breast, or lung cancer	≥20%	A	I	[21–23]	Non-inferior to filgrastim

^aNote further comments in the text.

SoR, strength of recommendation; QoE, quality of evidence.

Table 3. Other recommendations

Setting	Recommendation	SoR	QoE	References	Comment
G-CSF					
Adult patients with solid tumours	Start G-CSF early after chemotherapy	A	I	[28, 37–41]	
Adult patients with solid tumours	Start G-CSF at onset of neutropenia	C	II	[71]	Starting G-CSF after onset of neutropenia may be equally effective, but is not generally recommended due to lack of data
Adult and elderly patients with HL/NHL	Start G-CSF early after chemotherapy	A	I	[44–47]	
Adult patients with ALL undergoing induction or consolidation treatment	Start G-CSF early after chemotherapy	A	II	[52–54]	
Adult patients with ALL undergoing induction or consolidation treatment	Delay G-CSF until onset of neutropenia (max. d12)	C	II	[72]	Starting G-CSF after onset of neutropenia may be equally effective, but is not generally recommended due to lack of data
Elderly patients with AML undergoing induction chemotherapy	G-CSF delayed until 7 days after chemotherapy	C	II	[73]	No difference between starting G-CSF 1 day or 7 days after chemotherapy. G-CSF not generally recommended in this setting.
Adult patients developing FN after receiving chemotherapy without G-CSG support	Use G-CSF in following cycles	B	III	[74]	
Pegfilgrastim					
Adult patients with breast cancer	Use weight adapted dosing	B	II	[16]	Not generally recommended, confirmatory trials required
Adult patients with breast cancer	Start pegfilgrastim on day 2 of chemotherapy	A	I	[29, 75]	
Elderly patients with NHL, breast, or other cancer	Start with first cycle of chemotherapy, not wait until first febrile episode	A	I	[76]	
Elderly patients with NHL	Delay pegfilgrastim to day 4	B	II	[77]	

SoR, strength of recommendation; QoE, quality of evidence.

but not FN and was assigned to the high-risk group based on a 54% infection rate in the control group [41].

high risk for FN: >40%. Seven studies assessed G-CSF in high-risk patients (FN >40%) [37–41, 78, 80, 81, 83, 84]. Of these, five trials demonstrated a statistically and clinically significant reduction of FN or infection in the G-CSF group compared with the control group [37–41]. Three of these trials were placebo-controlled [37–39], and four were conducted in patients with SCLC [38–41], while one study assessed patients with sarcoma [37]. In the remaining two studies, the reduction of FN or infection in the G-CSF arm was not statistically significant [78, 84].

moderate risk for FN: 20%–40%. Three studies assessed G-CSF in moderate risk patients with SCLC [28], breast cancer [21], or metastatic germ-cell tumour [79]. In the study with SCLC patients (N = 186) [28], the risk for FN was significantly reduced from 32% in the control group to 18% in the G-CSF group (P = 0.01). In the studies in patients with germ-cell tumour [79] and breast cancer [21], the difference between treatment groups did not reach statistical significance.

low risk for FN: <20%. Two studies assessed G-CSF in patient with low-risk FN [42, 43]. In one large (N = 506) study with early-stage breast cancer patients, the risk for FN was reduced from 6.6% in the control group to 1.2% in the G-CSF group, P = 0.004 [43]. Another trial with ovarian cancer patients (N = 80) did not show a clinically or statistically significant difference in the incidence of FN between the treatment groups [42].

start of CSF in patients with solid tumours: In four RCTs, the influence of CSF timing was investigated [43, 71, 85, 86]. We excluded two of these studies published in Japanese only [85, 86]. One study compared three different schedules for administration of G-CSF in 33 patients with non-small-cell lung cancer [71]. No significant differences in terms of infectious complications were noted. One trial tested five different dosing regimens for G-CSF in breast cancer patients [43]. The authors reported no significant differences between any of these schedules. However, most landmark trials started G-CSF administration between 1 and 6 days after chemotherapy, and there are currently no sufficiently powered clinical trials to allow definite conclusions on the optimal timing of CSFs.

non-Hodgkin's lymphoma

We evaluated seven RCTs testing G-CSF as primary prophylaxis in patients with non-Hodgkin's lymphoma (NHL) undergoing myelosuppressive chemotherapy [44–46, 48, 87–89]. Two studies reported infection rates but not FN [46, 48]. One study [46] was rated high-risk study based on personal communication published elsewhere [90]. Another study lacking information on FN was categorised as reporting on intermediate risk patients given the 24% incidence rate of documented infection in the control group [48].

high risk for FN: >40%. Six RCTs were conducted in patients with high FN risk [44–46, 87–89]. Of these, two demonstrated a significant reduction of FN for patients receiving G-CSF (33% versus 50%, $P < 0.001$ [44], and 23% versus 44%, $P = 0.04$ [45]). Another two studies demonstrated a trend towards a reduced incidence of FN in the G-CSF group [87, 88]. Two relatively large ($N = 149$ and $N = 162$) RCTs with elderly (age >60 years) and adult NHL patients demonstrated a significantly reduced risk to develop documented infections [46, 87].

intermediate risk for FN: 20%–40%. One trial did not report the actual incidence of FN, but a 24% (41 of 168 cycles) to 4% (7 of 172) reduction of documented infections by G-CSF administration [48]. The P value was not reported.

Hodgkin's lymphoma

We identified one RCT assessing G-CSF [47] in patients with Hodgkin's lymphoma (HL). This study was conducted in patients with high risk (43%) for FN [47], but failed to prove a reduction of infectious complications in HL patients undergoing standard chemotherapy, probably due to the low power. There were no RCTs in elderly HL patients.

comment on recommendation. There are no RCTs demonstrating a benefit of G-CSF usage in HL. However, based on panel opinion, results from the NHL trials probably apply to HL as well. G-CSF use was recommended for patients with a high ($\geq 40\%$) or intermediate risk (20%–40%) of FN.

start of CSF in malignant lymphoma: No study was identified that compared different starting points in patients with malignant lymphoma. Most landmark trials started G-CSF administration between 2 and 6 days after chemotherapy, and there are currently no sufficiently powered trials to allow definite conclusions on the optimal timing of CSFs.

myelodysplastic syndrome

One RCT exploring the use of G-CSF in patients receiving palliative chemotherapy was identified. In this trial, severe infections (WHO III, IV) occurred more frequently in G-CSF recipients compared with controls; however, the difference was not significant (30% versus 19%, P not reported) [50]. The incidence of FN was not reported.

acute lymphoblastic leukaemia

limitations. In several studies evaluating G-CSF in patients with acute leukaemia, the effects of G-CSF are reported

separately for induction and consolidation therapy. We have therefore reported both single-study cycles and summary results separately in the evidence tables.

induction and consolidation therapy: Five RCTs using G-CSF as primary prophylaxis in patients with acute lymphoblastic leukaemia (ALL) during induction or consolidation therapy were identified [52–54, 91, 92]. Only one of the analysed studies reported the incidence of FN (42% in the control arm, high risk) [53]. Another three studies were classified as high-risk group (FN >40%) based on the incidence of fever and infections [52, 53, 91, 92].

high risk for FN: >40%. Of the above-mentioned G-CSF trials, only one open-label RCT demonstrated significant reduction of documented infections for patients receiving G-CSF (40% versus 77%, $P = 0.017$) [53]. The same study was the only to report FN, which was significantly reduced in the G-CSF arm (12% versus 42%, $P = 0.035$) [53]. One RCT demonstrated a significant reduction of the total incidence of infections for patients receiving G-CSF during induction (3% versus 28%, $P = 0.01$) [54]. A third trial did not demonstrate a significant reduction of infections during induction or consolidation; however, the overall number of infections was significantly reduced (61% versus 84%, $P < 0.05$) [52]. Fever was reported in two studies, both studies failed to show a statistically significant reduction of fever in the G-CSF group [91, 92].

start of CSF in ALL during induction and consolidation: In two small controlled clinical studies, the influence of CSF starting time was investigated [72, 93]. One of these studies demonstrated a significantly reduced incidence of documented infections for patients receiving G-CSF at day 4 compared with day 15 of induction therapy (35% versus 71%, $N = 80$, $P = 0.007$) [72]. A second RCT ($N = 55$) did not demonstrate a difference between starting 12 versus day 17 of consolidation therapy [93]. Trials comparing G-CSF administration with placebo started treatment between 2 and 9 days after chemotherapy. There are currently no sufficiently powered trials to allow definite conclusions on the optimal timing of CSFs.

acute myeloid leukaemia

elderly patients. We evaluated three studies comparing G-CSF [62–64] to placebo or control in elderly patients undergoing induction therapy for acute myeloid leukaemia (AML). Definitions for elderly patients were inconsistent across studies and ranged from ≥ 55 years [62] to ≥ 65 years [63]. On average, the mean/median age of the included patients was 68 years, range 56–88 years. No study on consolidation therapy alone was identified. None of the studies reported the incidence of FN.

high risk for FN: >40%. There were two RCTs comparing G-CSF with placebo [62, 63]. Both studies failed to demonstrate a reduced incidence of severe infection, bacteraemia, mycoses, or pneumonia in patients receiving G-CSF compared with controls [62, 63]. Fever or FN rates were not reported.

moderate risk for FN: 20%–40%. One open-label RCT [64] did not provide evidence for a reduced incidence of severe

infections in patients receiving G-CSF compared with controls. Fever or FN rates were not reported.

start of CSF: There was one study directly comparing different starting points for prophylactic application of G-CSF in elderly AML patients undergoing induction therapy [94]. The study included 66 elderly patients with risk factors who were receiving remission-induction chemotherapy with a reduced dose. Patients were randomised to receive G-CSF 1 day after end of chemotherapy (early), or 7 days after end of chemotherapy (late). During the first cycle of induction chemotherapy, there was no difference between the percentage of patients with FN (early 83% versus late 69%, $P = 0.22$). There was no difference in the duration of neutropenia and the number of febrile days between the two groups.

adult patients or patient groups with AML not restricted to elderly

We evaluated eight RCTs comparing G-CSF [55–61, 95] prophylaxis during induction or consolidation chemotherapy for treatment of AML. None of the studies reported FN; all but one study were categorised based on the reported incidences of infections [55–60]. The remaining study could not be categorised [61].

high risk for FN: >40%. Five studies evaluated G-CSF prophylaxis during aggressive remission induction [55–58, 60]. None of the trials showed a reduction of infection rates. Two studies assessed G-CSF during consolidation [55, 59]. Among a number of variables tested, Harousseau et al. demonstrated a possible reduction of septicaemia for patients receiving G-CSF during the second consolidation (25% versus 31%, $P = 0.05$) [59]. Heil et al. analysed the incidence of fever by multiple testing after each chemotherapy cycle and reported a statistically significant reduction in the G-CSF group only during the first consolidation, but not after the induction chemotherapies or after the second consolidation [55].

pegfilgrastim compared with filgrastim—solid tumours

Three trials investigated the effectiveness of pegfilgrastim in patients with breast cancer compared with filgrastim [15–17]. We excluded another study for not reporting data for FN or infections [14]. For all three trials, FN rate for categorisation into one of the FN risk groups was extrapolated from the literature for lack of a placebo control arm. Given a FN rate of 24% [95% confidence interval (CI) 18% to 30%] in a comparable trial [96], the patients from the identified studies can approximately be categorised as moderate FN risk [15–17].

Of the included breast cancer studies, none reported infections, but all reported FN rates. One non-inferiority trial assessing 296 breast cancer patients undergoing chemotherapy with or without a weight-based dose of 100 µg/kg pegfilgrastim per cycle versus daily G-CSF demonstrated a significant ($P = 0.029$) reduction of FN compared with filgrastim (9% versus 18%) [15]. A second smaller trial with a similar study design found similar FN rates in patients receiving pegfilgrastim and in patients receiving filgrastim [16]. The third trial assessing 152 breast

cancer patients undergoing chemotherapy with fixed dose of pegfilgrastim (6 mg per cycle subcutaneous) compared with G-CSF, showed a lower rate of FN in pegfilgrastim recipients; however, the difference was not statistically significant (13% versus 20%, $P = \text{NS}$) [17].

pegfilgrastim compared with placebo—solid tumours

One trial assessed 928 breast cancer patients receiving intensified docetaxel (100 mg/m²) chemotherapy supported with 6 mg pegfilgrastim per cycle or placebo [29]. Patients who developed FN were allowed to take antibiotic prophylaxis for the subsequent cycles. The incidence of FN was significantly reduced from 17% in the control arm to 1% in the pegfilgrastim arm ($P < 0.001$). Given the rate of FN close to 20%, it was decided to categorise this study as moderate FN risk. Another trial reported on 252 patients receiving FOLFOX, FOLFIRI, or FOIL chemotherapy for colorectal cancer received with pegfilgrastim 6 mg or placebo [70]. Across all cycles, the incidence of FN was reduced from 8% to 2% by pegfilgrastim ($P = 0.04$).

start of pegfilgrastim—solid tumours

A randomised trial in 351 female node-positive breast cancer patients receiving chemotherapy compared administration of pegfilgrastim 6 mg with weight adaptation for obese patients on day 2 versus day 4 of chemotherapy [75]. The authors reported no difference between both strategies along a number of infection-related end points, including FN.

pegfilgrastim compared with filgrastim—haematological malignancies

Three RCTs analysed the effectiveness of pegfilgrastim compared with G-CSF in patients with haematological malignancies [18–20]. For lack of a control arm without CSF prophylaxis, FN rate in the Vose study [18] was extrapolated as moderate risk from a study published by Velasquez et al. [97], in which the FN rate was 30%. By the same approach, the study published by Grigg et al. [19] was categorised as reporting on high-risk chemotherapy based on observations by Ösby et al. [44]. The study by Sierra et al. [20] was also categorised as high risk. For all three trials, FN rates, but no infection rates, were reported.

high risk for FN: >40%. Two studies [19, 20] investigated the effect of pegfilgrastim versus filgrastim in patients with high risk for FN. Grigg et al. investigated the effect of pegfilgrastim (60 µg/kg or 100 µg/kg per cycle) compared with filgrastim (5 µg/kg/day) in 49 elderly patients with NHL [19]. The observed rates of FN were not significantly different. Sierra et al. investigated the effect of 6 mg pegfilgrastim once per cycle versus 5 µg/kg filgrastim daily in 84 adult AML patients [20], also with no significant differences observed.

moderate risk for FN: 20%–40%. In one moderate risk trial, 60 patients with relapsed and refractory malignant lymphoma (HL and NHL) underwent myelosuppressive chemotherapy [18]. Patients received one weight-based dose of 100 mg/kg of pegfilgrastim per cycle sc or daily G-CSF injections. Cumulative incidences of FN were not significantly different between

treatment arms (21% in pegfilgrastim arm, 19% in G-CSF arm, $P = \text{NS}$).

start of pegfilgrastim—haematological malignancies

One trial in 109 elderly patients with aggressive lymphomas receiving R-CHOP-14 chemotherapy randomised administration of pegfilgrastim 6 mg between day 2 and day 4. Grade 3 or 4 infections were 9.4% after day 2 administration and 6.0% after day 4 administration (not significant) [77].

biosimilar G-CSF XM02

We identified three RCTs [21–23] investigating the efficacy of identical doses of XM02 and filgrastim in patients with NHL receiving CHOP chemotherapy [22], lung cancer patients receiving a platinum-based chemotherapy [23], and breast cancer patients receiving doxorubicin and docetaxel [21]. XM02 was non-inferior to filgrastim in all three trials [21–23].

use of GM-CSF for primary prevention of infections

In contrast to G-CSF, GM-CSF is acting on macrophages as well. G-CSF and GM-CSF are probably comparable regarding tolerability and efficacy in decreasing incidence and duration of neutropenia and fever after standard dose chemotherapy, although there is a lack of formal comparisons between both drugs [73, 98–102]. Numerous clinical trials have been conducted using GM-CSF for the primary prophylaxis of FN by GM-CSF administration. Clinical trials in patients with solid tumours, NHL, MDS, ALL, AML, and MDS were identified and evaluated. Taken together, the overall quality of evidence of was lower than for G-CSF, and none of the trials demonstrated a marked benefit of GM-CSF compared with G-CSF. However, GM-CSF is no longer commercially available in Germany and several other European countries. For these reasons, GM-CSF has not received a recommendation in this guideline. The reviewed evidence is detailed in supplementary File 03, available at *Annals of Oncology* online.

other treatment strategies

We identified one RCT that compared ‘proactive’ versus ‘reactive’ pegfilgrastim prophylaxis in 862 elderly (aged >65 years) patients with breast cancer, NHL, or other cancer undergoing chemotherapy [76]. Patients were randomised to ‘proactive’ management starting pegfilgrastim in the first cycle of chemotherapy or ‘reactive’ management, i.e. not giving pegfilgrastim in the first cycle and based on the discretion of the attending physician in the subsequent chemotherapy cycles. After six cycles of chemotherapy, the incidence of FN in patients with solid tumours was 4% in the proactive study arm and 10% in the reactive study arm ($P = 0.01$). In the considerably smaller group of NHL patients, 15% in the proactive arm and 37% in the reactive arm contracted FN ($P = 0.004$).

conclusion

In our review, we found convincing evidence from numerous randomised, controlled trials that G-CSF, biosimilar G-CSF, and pegfilgrastim reduce the risk to develop FN and infections. As a rule of thumb, it seems the relative benefit is highest for patients with an intermediate risk of infections. For patients with long-term neutropenia, e.g. after induction-chemotherapy for AML, the slightly shorter duration of the at-risk period does not seem to translate into a clinical benefit [55–64]. On the other hand, in patients with a low baseline risk in whom infections often can be treated in an outpatient setting [5], the number needed to treat to achieve a meaningful benefit is probably high [70].

Our comprehensive literature search and expert panel consensus confirmed many key recommendations given guidelines of other working groups [32, 34]. However, compared with other guidelines, we rated the evidence for growth factors during AML induction chemotherapy and pegfilgrastim use in haematological malignancies lower.

Treatment with G-CSF is associated with substantial costs [103] and some adverse events. The long-term safety of G-CSF remains a matter of debate [104, 105]. Although not formally part of this review, both factors must be weighed against the potential benefits of G-CSF treatment. While preventing fever and infection may reduce the need for hospitalisation and antibiotic treatment [106] as well as promote timely continuation of following chemotherapy cycles [70], a clear benefit for overall survival or tumour response has not been demonstrated, and data on cost-effectiveness is controversial [103, 107].

Taken together, G-CSF is a supportive drug that can improve overall conduct of chemotherapy and patient care in certain scenarios, though probably not vital for treatment success in most cases.

funding

The AGIHO is supported by unrestricted grants from Amgen, Pfizer, MSD, and Gilead. AB has received research sponsoring from TEVA. JJV has received research grants from Astellas, Gilead, Merck, and Pfizer. OAC is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106) and has received research grants from Actelion, Astellas, Basilea, Bayer, Biocryst, Celgene, F2G, Genzyme, Gilead, Merck/Schering, Miltenyi, Optimer, Pfizer, Quintiles, and Viropharma. MJGTV received research funding from 3M. OP has received research funding from Bio Rad, Fresenius biotech, Gentium, Genzyme, Gilead, Pierre Fabre. This review was carried out and written by academic authors without external support or funding.

disclosure

JJV has been a speaker for Astellas, Gilead, Merck, and Pfizer, has been a consultant to Astellas, Merck, and Pfizer, and has received travel grants from Astellas, Gilead, Merck, and Pfizer. OAC is a consultant to Astellas, Basilea, F2G, Gilead, Merck/Schering, Optimer, and Pfizer, and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. MJGTV has served at the speakers’ bureau of Pfizer, Merck, Gilead Sciences,

and Astellas Pharma. OP has been a consultant to MSD, and received lectures and travel grants from Astellas, Gilead, Pfizer, and MSD. CK, MK, KAK, GM, SM, VO, and JB have no conflicts of interest to declare.

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