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SEOM clinical guidelines for myeloid growth factors

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Abstract Neutropenia induced by chemotherapy (CT) is an infection risk factor associated to greater morbidity/mortality and dose-limiting toxicity that on many occasions requires a reduction of the dose of cytostatics or a delay in the administration of treatment. This may have a negative effect on the patient's quality of life and even diminish the efficacy of the treatment, especially when the intention is to cure or prolong survival. Management of treatment or prophylaxis of grade 3–4 neutropenia and febrile neutropenia with myeloid growth factors (CSF) varies very much in clinical practice, both in the time of starting treatment and the types of patients it is given to. The need to generalise and facilitate practice based on clinical evidence has led the Spanish Society of Medical Oncology (SEOM) to prepare clinical practice guidelines on the use of myeloid growth factors.

Keywords Neutropenia · Febrile neutropenia · Myeloid growth factors · G-CSF · Clinical practice guidelines · Filgrastim · Pegfilgrastim

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Introduction

For years, myelosuppression associated to chemotherapy (CT) has been a major limitation of patient tolerance to antineoplastic treatment. Moreover, the clinical consequences of this myelosuppression (increased risk of infection leading to greater morbidity and mortality, rise in hospital admissions, reduction of cytostatics dose or delayed administration of CT) can have a negative effect on the quality of life of patients or even diminish treatment efficacy and patient survival.

At present, there are molecules capable of stimulating growth, survival and differentiation of the myeloid progenitor cells, as well as functional activation of their mature cells. This family of molecules is called haematopoietic growth factors (hGFs), colony-stimulating factors (CSFs) or haematopoietic cytokines. Table 1 shows all recombinant human myelopoietic growth factors approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for clinical use.

Benefits of treatment with CSF

From the randomised clinical trials with CSFs and the various meta-analyses conducted, we can conclude the following about adjuvant therapy with CSF:

- It reduces the incidence, duration and severity of CT-induced neutropenia in solid and haematological tumours (small lung cancer, breast cancer, sarcomas and non-Hodgkin's lymphomas) [1–4].
- It allows the administration of full doses of CT, the possibility of completing the number of cycles planned, and increasing the intensity or density of doses, improving therapeutic response, tumour control and survival of patients with breast cancer [5, 6], high-grade lymphomas [7], lung cancer [8] and ovarian cancer [9].
- It reduces the cost of febrile neutropenia (FN) by diminishing the number of hospitalisations and the

Table 1 hGFs for clinical use in the treatment of cancer

Growth factor (gene locus)	Brand name	Dose and administration regimen
G-CSF (17q11-21)		
Filgrastim	Neupogen[a]	5 μg/kg/day SC. Dose may be adjusted to the preloaded 30-million IU (300 μg) or 48-million IU (480 μg) syringes.
Filgrastim (XM02)[b]	Ratiograstim[a]	0.5 million IU/kg/day SC or in 30-min IV perfusion. Dose may be adjusted to the preloaded 30-million IU (0.5 ml) syringes.
	Biograstim	
	Tevagrastim	Preloaded 30 million IU (0.5 ml) or 48 IU (0.8 ml) syringes.
Filgrastim (EP2006)[b]	filgrastim Zarzio[a] filgrastim Hexal	Preloaded 30 million IU (0.5 ml) or 48 IU (0.8 ml) syringes.
Lenograstim	Granocyte[a]	19.2 million IU/m^2/day SC. Dose may be adjusted to the preloaded 13.4-million IU (105 μg) or 34-million IU (263 μg) syringes.
Pegfilgrastim	Neulasta[a]	Preloaded 6 mg pen SC 3qw or 2qw.
GM-CSF (5q31.1)		
Sargramostim	Leukine[a]	250 μg/m^2/day SC.
Molgramostim	Macrogen	5 μg/kg/day SC. Dose may be adjusted to the preloaded 4.4×106 IU (equivalent to 400 μg) syringes.

SC, subcutaneous route of administration; IU, international units; 2qw, every 2 weeks; 3qw, every 3 weeks
[a]Drugs approved in Spain
[b]Drug biosimilar to filgrastim

need for intravenous antibiotics during CT treatment [10, 11].
- Two meta-analyses [12, 13], of studies published up to 2007, confirmed the efficacy of prophylaxis with CSFs in diminishing the rate of infections and the risk of neutropenia and FN during CT, but no significant benefit was found in terms of tumour response and survival.
- Another meta-analysis [14], of 17 randomised clinical trials and 3493 patients with solid tumours and lymphoma, shows that primary prophylaxis with G-CSF reduces the risk of FN (RR: 0.54; CI 95%: 0.43–0.67); increases the intensity of the CT dose administered (difference of 8.4%; p=0.001); and, for the first time, reduces the risk of death related to infection (RR=0.55; CI 95%: 0.33–0.90) and the risk of early death during CT (RR=0.60; CI 95%: 0.43–0.83).

Use of CSFs to support conventional chemotherapy

The use of CSFs to support CT may have a prophylactic purpose, to prevent the onset of FN, or a therapeutic one, to treat an episode of FN documented in a patient who has not received CSFs previously.

Primary prophylaxis

This is defined as the use of CSFs to prevent the onset of FN during the first cycle of CT, when no episode has yet occurred, based on the risk of suffering an episode of FN (see Table 2, Fig. 1).

The need for support with G-CSF must be evaluated individually before each cycle of CT in order to assess the overall risk of FN. This assessment must take into account not only the type of CT but also individual patient factors that may increase the risk of FN and the aim of the treatment to be administered. This assessment process can be conducted in four steps (Fig. 1):

Step 1: Identify the risk of FN associated to the chemotherapy regime chosen

CT regimes can be classified into risk groups according to the incidence of FN published in clinical trials (Table 2). Nonetheless, it should be noted that the rates of neutropenia and FN reported in the clinical trials with equal or similar CT regimes vary greatly, which hinders a true and real assessment of the risk of FN and related complications associated to a specific CT regimen [15]. This variability can be a reflection of differences in the patient populations studied as well as in the intensity of the actual dose administered in each clinical trial.
- CT regimens with risk of FN >20%: primary prophylaxis with CSF is recommended.
- Regimens with risk of FN between 10 and 20%: primary prophylaxis with G-CSF should be considered in patients with risk factors.
- Regimens with risk of FN <10%: prophylaxis with CSF is not recommended.

As appropriate, prophylactic CSF should be given to allow administration of dense-dose and intensive-dose regimens. Administration of prophylactic CSF may be considered to maintain the CT dose and minimise delays when reduction and delay of a dose is associated to poor prognosis.

Table 2 CT regimens by risk of FN

Tumour type	FN risk category	CT regimen	FN risk (%)
Breast cancer	>20%	AC→docetaxel	5–25
		Docetaxel→AC	40
		Doxorubicin/docetaxel	33–48
		Doxorubicin/paclitaxel	21–32
		TAC	22–25 (no PP)
		DD/DDG FEC	71/59
		FEC-docetaxel	25–46
		DDG doxorubicin→paclitaxel→cyclophosphamide	2 (with PP)
		DDG doxorubicin/cyclophosphamide→paclitaxel	2 (with PP)
		DDG epirubicin/cyclophosphamide	8 (with PP)
	10–20%	Doxorubicin/vinorelbine	15
		Docetaxel	16–17
		Capecitabine/docetaxel	13
		Cyclophosphamide/mitoxantrone	11
		FEC-100	13–17 (with PP)
		AC	14
		Epidoxorubicin/cyclophosphamide	13
		CEF	14
		FEC 120	9–14
	<10%	CMF	0–3
		Oral CMF	1
		Doxorubicin/cyclophosphamide	0–3
		Doxorubicin→paclitaxel→cyclophosphamide	3
		Doxorubicin/cyclophosphamide→paclitaxel	5
		FAC 50	5
		Epirubicin/cyclophosphamide±lonidamine	7
Small-cell lung cancer	>20	Etoposide/cisplatin	54
		ACE	24–57
		Topotecan	28
		ICE	24
		VICE	70
		DDG ACE	34–56
		DDG ICE	18
		DDG CAV→PE	4
	10–20	CAV	14
		Etoposide/carboplatin	10–20
		Topotecan/cisplatin	19
		Tirapazamine/cisplatin/etoposide/irradiation	14
		CODE	19
	<10	CAV→PE	3–9
		Paclitaxel/carboplatin	9
Non-small-cell lung cancer	>20	Docetaxel/carboplatin	26
		Etoposide/cisplatin	54
		Cisplatin/vinorelbine/cetuximab	22
		VIG	25
	10–20	Paclitaxel/cisplatin	16
		Docetaxel/cisplatin	5–11
		Vinorelbine/cisplatin	1–10
	<10	Paclitaxel/carboplatin	0–9
		Gemcitabine/cisplatin	1–7
		Bevacizumab/paclitaxel/carboplatin	5.2
Ovarian cancer	>20%	Docetaxel	33
		Paclitaxel	22
	10–20%	Topotecan	10–18
	<10%	Paclitaxel/carboplatin	3–8
		Gemcitabine/cisplatin	9
Urothelial cancer	>20%	Paclitaxel/carboplatin	25
		MVAC	26
		DDG MVAC	10
Germinal tumours	>20%	BOP→VIP-B	46
		VeIP	67
	10–20%	Cisplatin/etoposide 43,183	10
		BEP→EP	13

Table 2 *(Continuation)*

Tumour type	FN risk category	CT regimen	FN risk (%)
Colon and rectal cancer	10–20%	5-FU/leucovorin	1–15
		FOLFIRI	3–14
	<10%	FOLFOX	0–8
		IFL	3–7
		Irinotecan	2–7
Gastric cancer	>20%	LVFU-cisplatin	40
		DCF (docetaxel/cisplatin/fluorouracil)	29
		LVFU-irinotecan	24
		TC (docetaxel/cyclophosphamide)	21
		TCF (docetaxel/cyclophosphamide/fluorouracil)	41
	10–20%	ECF (epirubicin/cisplatin/fluorouracil)	18
		Docetaxel-irinotecan	14.9
		FOLFOX-6	11
Oesophagus cancer	10–20%	ECF (epirubicin/cisplatin/fluorouracil)	13.2
		ECX (epirubicin/cisplatin/capecitabine)	10.5
		EOF (epirubicin/oxaliplatin/fluorouracil)	11.5
		EOX (epirubicin/oxaliplatin/capecitabine)	9.8
Other tumours	>20%	TIC (head and neck)	30
		TPF (head and neck)	19
		MAID (sarcoma)	58
		Paclitaxel/cisplatin (cervical cancer)	28
	10–20%	Gemcitabine/irinotecan (pancreatic cancer)	17
	<10%	Doxorubicin/cisplatin (endometrial cancer)	2
		TAP (endometrial cancer)	3
Non-Hodgkin's lymphoma/chronic lymphocytic leukaemia	>20%	DHAP	48
		ESHAP	30–64
		R-ESHAP	33.5
		CHOP-21	17–50
		DD/DDG VAPEC-B	23–44
		DD/DDG ACVBP	52–78
		Hyper CVAD+rituximab	52–78
		ICE/R-ICE	11.5–24 with PP
		Stanford V	Neutropenia G 3–4: 25%
		MOPPEB-VCAD	Neutropenia G 3–4: 49%
		FC (fludarabine/cyclophosphamide)	35
		FC-rituximab	Neutropenia G 3–4: 33.7%
	10–20%	ACOD	11
		R-CHOP-21	19
		Fludarabine/mitoxantrone	11
		EPOCH with adjusted dose	19% of cycles
		Mega CHOP-R-Ara-C	15
		RGemP	Neutropenia G 3–4: 61%
		RGemOx (elderly patients)	Neutropenia G 3–4: 43%
Hodgkin's disease due to sepsis: 10%	>20%	BEACOPP	Neutropenia G 4: >90% deaths
		ABVD (Hodgkin's lymphoma)	4
		CEC	Neutropenia G 3–4: 48%
		IGEV	Neutropenia G 3–4: 28%

Adapted from Ref. [35]

PP, primary prophylaxis; DD, dose-dense; DDG, dose-dense with G-CSF; ACE, doxorubicin, cyclophosphamide and etoposide; ICE, ifosfamide, carboplatin and etoposide; VICE, vincristine, ifosfamide, carboplatin and etoposide; CAV, cyclophosphamide, doxorubicin and vincristine; VIG, vinorelbine, ifosfamide and gemcitabine; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; BOP, bleomycin, vincristine, cisplatin; VIP-B, cisplatin, ifosfamide, etoposide, bleomycin; VelP, vinblastine, ifosfamide, cisplatin; BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; TIC, paclitaxel, ifosfamide, carboplatin; TPF, cisplatin, docetaxel, 5FU; MAID, mesna, adriamycin, ifosfamide, dacarbazine; TAP, paclitaxel, doxorubicin, cisplatin; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ACOD, doxorubicin, cyclophosphamide, vincristine and prednisolone; ACVBP, doxorubicin or mitoxantrone with cyclophosphamide, vindesine and bleomycin; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; CHOP-21, cyclophosphamide, doxorubicin, vincristine and prednisone; CVAD, cyclophosphamide, vincristine, adriamycin and dexamethasone; DHAP, cisplatin, cytarabine and dexamethasone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; Hyper CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; IGEV, ifosfamide/Mesna, gemcitabine and vinorelbine; RGemP, rituximab, gemcitabine and methylprednisolone; RGemOx, rituximab, gemcitabine and oxaliplatin; R/ICE, ifosfamide, carboplatin, etoposide and rituximab

Step 2: Identify patient-related risk factors that may increase the risk of FN

There are certain patient circumstances or characteristics that may increase the risk of infectious complications or FN in which the use of CSF would be indicated even when the risk of FN with the regimen used is less than 20%:

Factors associated to a high risk of FN (evidence level I):

- Age ≥65

Factors associated to an increase in the risk of FN (evidence level I and II):

- Previous episode(s) of FN
- Advanced stages of the disease
- No previous use of G-CSF or prior antibiotic prophylaxis

Other FN risk factors (evidence level III and IV):

- Poor performance and/or nutritional status
- Female gender
- Haemoglobin level <12 g/dl
- Severe comorbidities, especially renal, liver or cardiovascular disease
- Prior history of extensive CT or prior irradiation of the pelvis or other areas with a high content of bone marrow
- Tumour infiltration of bone marrow
- Existence of open wounds or active infections
- Recent surgery
- Combined chemoradiotherapy

Step 3: Define overall risk of FN

Assessment of the overall risk of FN should be done individually for each patient and before the start of treatment considering the CT regimen and associated risk factors.

High overall risk (>20%): Primary prophylaxis with CSF is indicated.

Medium overall risk (10–20%): Primary prophylaxis with G-CSF recommended according to treatment aim.

Low overall risk (<10%): Prophylaxis with CSF not recommended.

Step 4: Consider treatment aim, which may help with the decision to use primary prophylaxis with G-CSF

There are three situations or treatment aims to be considered: curative or adjuvant; to prolong survival; and palliative and to control symptoms. The recommendation of prophylactic use of CSF is based on the overall risk of FN and the treatment aim (Fig. 1). In general:

Patient with high overall risk of FN (>20%): Primary prophylaxis with CSF recommended with evidence level 1 if treatment aim is curative, adjuvant or to prolong survival. In a palliative situation or to control the symptoms, prophylactic use of CSF may be considered if the patient presents risk factors. If the risk is determined only by the CT regimen, other alternatives should be explored, such as reducing the dose or changing to a less myelotoxic regimen.

Medium overall risk (10–20%): Primary prophylaxis with G-CSF is indicated when the treatment aim is curative or adjuvant; it would also be indicated if the treatment aim is to prolong patient survival. Nonetheless, when the aim is only to control symptoms, primary prophylaxis may be indicated if the risk is determined by the presence of poor prognosis factors and not by the CT regimen.

Low overall risk (<10%): Prophylaxis with CSF is not recommended; nonetheless, when the aim is curative or adjuvant, prophylaxis may be considered if the patient has a significant risk of severe medical complications as a result of FN, including death.

Secondary prophylaxis

Defined as the use of CSFs to prevent subsequent episodes of FN or dose-limiting neutropenia in patients who have already presented a first episode during a prior cycle.

Following an episode of FN or dose-limiting neutropenia, secondary prophylaxis with CSF should be considered in the following CT cycle:

- If CSF has not been administered previously.
- In cases in which a reduction or delay of the dose is associated to poor prognosis.

Therapeutic use

Defined as the use of CSF in patients presenting an episode of neutropenic fever. Compared to prophylactic use, there is less scientific evidence supporting the therapeutic use of CSFs as adjuvants of antibiotics in the treatment of FN.

Two meta-analyses [16, 17] and a recent randomised trial [18] prove that the use of CSF in the treatment of FN reduces duration of neutropenia, hospital stay and the use of IV antibiotics in patients who received CSF, but no decrease was observed in mortality secondary to infections or an increase in overall survival.

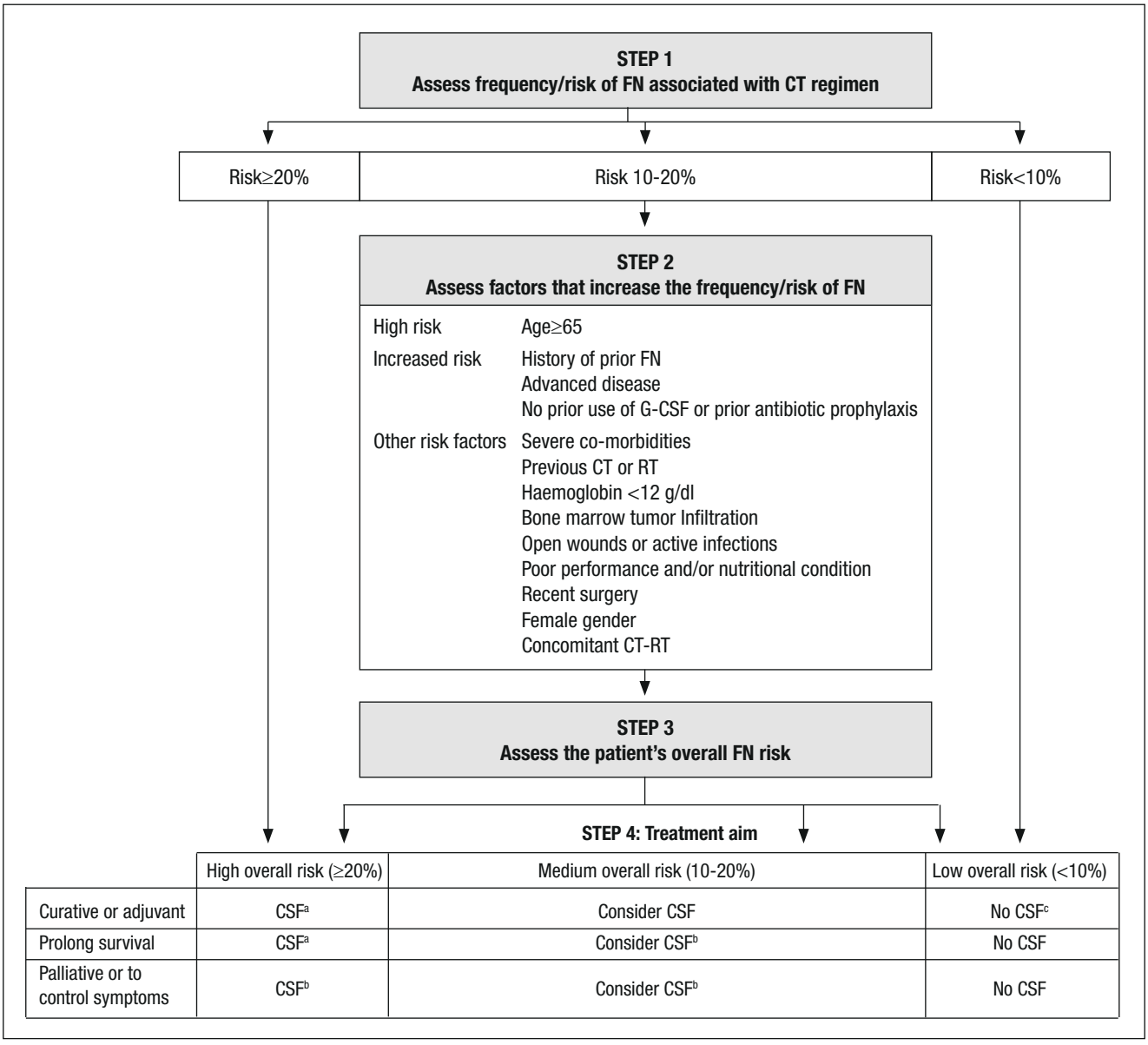
When faced with an episode of FN, three situations are possible:

Patients who have received prophylaxis with CSF (filgrastim, lenograstim or sargramostim) should continue with therapeutic CSF.

Patients who have received prophylaxis with pegylated CSF (pegfilgrastrim) should not be treated with additional CSF.

Patients who have not received prophylaxis with CSF. Therapeutic use of CSF is recommended based on the existing risk factors for poor clinical outcomes or for developing infection-associated complications. These factors include: age >65; sepsis syndrome; severe neutropenia (absolute neutrophil count (ANC) <100/μl) or prolonged neutropenia duration (>10 days); pneumonia, invasive fungal infection, other clinically documented infections; hospitalisation at the time of fever and prior episode of FN.

- If the patient presents risk factors for developing infection-associated complications, treatment with CSF should be considered.



	High overall risk (≥20%)	Medium overall risk (10-20%)	Low overall risk (<10%)
Curative or adjuvant	CSF[a]	Consider CSF	No CSF[c]
Prolong survival	CSF[a]	Consider CSF[b]	No CSF
Palliative or to control symptoms	CSF[b]	Consider CSF[b]	No CSF

Fig. 1 Algorithm for use of CSF in primary prophylaxis. [a]Evidence level 1 for G-CSF. [b]If risk is determined by the presence of poor prognosis factors, use of CSF is reasonable; but if risk is determined only by CT regime, other alternatives should be explored such as reducing the dose or switching to a less myelotoxic regime. [c]Prophylaxis may be considered if the patient has a significant risk of severe medical complications as a result of neutropenic fever, including death

– If the patient presents no risk factors, treatment with CSF is not recommended.

Given the lack of sufficient evidence on the therapeutic use of pegfilgrastrim, only filgrastim or sargramostim should be used for the treatment of FN.

Types and administration of CSFs

While randomised studies with filgrastim, lenograstim and pegfilgrastim focused on patients with solid tumours and lymphomas providing evidence for their use, clinical trials with sargramostim have focused on its use in induction therapy of myeloid leukaemia and haematopoietic progenitor cell transplants. Therefore, in adjuvant treatment of solid tumours and lymphomas, the CSF of choice should be filgrastim, lenograstim or pegfilgrastim (evidence level I) and alternatively sargramostim (evidence level II) (see Table 1).

A meta-analysis [16], a systematic Cochrane review [12] and several randomised clinical trials show that daily administration of G-CSF (filgrastim and lenograstim) and GM-CSF (sargramostim and molgramostim) is comparable in efficacy. Likewise, filgrastim and lenograstim have similar efficacy in the prevention and treatment of FN.

General principles

The administration route of choice of the various CSFs is subcutaneous.

Administration of CSF on the same day of CT is not recommended. Several studies have observed an increase in the incidence of FN and adverse events in patients starting administration of CSF on the same day of CT [19, 20].

Interrupting treatment with CSFs after recovery of neutrophils is sometimes accompanied by a decrease in the ANC, approximately 50% a day, returning to baseline values in 4–6 days. This drop in neutrophils is less pronounced with GM-CSF and the pegylated form of G-CSF.

It is not recommendable to initiate a new cycle of CT until at least 24 h have elapsed since completion of treatment with CSFs, given that highly mitotic cells (such as progenitor cells) may present greater sensitivity to CT [21].

Likewise, simultaneous administration of CSFs in concomitant chemoradiotherapy may entail greater haematological toxicity, specially thrombocytopenia, a higher number of toxic deaths, greater use of antibiotics and longer hospital stays [22, 23]. In the absence of CT, for patients receiving radiotherapy in large areas (mediastinum, abdomen, pelvis, etc.), use of CSFs may be considered if prolonged treatment delays are expected due to neutropenia.

Filgrastim

Administration of filgrastim (G-CSF) should start between 24 and 72 h after completing CT with a daily dose of 5 μg/kg and it should be maintained until neutrophils recover to normal or close to normal figures (≥1500/mm^3).

Administration of CSF for a set period of 5 or 7 days is also efficacious and safe [24, 25]. However, several observational studies published recently [26–28], indicate that ≥7 days of G-CSF is more effective than <7 days to reduce the risk of FN, the risk of hospitalisation, the incidence of infectious complications and use of antibiotics.

It has been noted that delaying the start of administration of daily G-CSF (>72 h) increases the depth and duration of the ANC nadir, delays recovery of ANC, increases duration of grade 4 neutropenia, and increases the incidence and duration of FN [29, 30].

The dose of filgrastim can be rounded off or adjusted to the dose of the marketed vials according to the patient's weight (Table 1).

Recently, two filgrastim biosimilar agents have been approved in Europe: XM02 and EP2006 (see Table 1). A meta-analysis of 3 randomised trials shows that filgrastim XM02 is similar in efficacy to filgrastim [31]. A phase III study that includes pharmacodynamics and pharmacokinetics data shows that filgrastim EP2006 is similar to filgrastim [32]. Given that a biosimilar product is not a generic drug, switching filgrastim for a biosimilar product implies a treatment change. Given the multiple variations in the production process, biological products tend to differ from one another. Consequently, to assure traceability and pharmacovigilance of these biological products, they must be identified by their brand name and it should be ascertained that no treatment changes are made without our and/or the patient's consent.

Pegfilgrastim

The pegylated form of G-CSF, pegfilgrastim, should be administered 24 h after completing CT, once every 21 days, in a single 6-mg dose per treatment cycle. There is not sufficient evidence at present to recommend the use of pegfilgrastim in weekly regimens or administrations of less than 2 weeks.

Pegfilgrastim was similar to filgrastim in the registration trials, but a combined post hoc analysis of these studies suggests that pegfilgrastim is significantly better to reduce the incidence of FN than filgrastim (RR 0.56; CI 95%: 0.35–0.89) [33]. In a meta-analysis of 5 randomised clinical trials, pegfilgrastim reduced the risk of FN 36% more than filgrastim (RR 0.64; CI 95%: 0.43–0.96) [34].

Sargramostim

Administration of sargramostim (GM-CSF) should be started 24–72 h after completing CT in a daily dose of 250 μg/m^2 and it should be maintained until recovery of normal or nearly normal neutrophil values (≥1500/mm^3). The dose of sargramostim can also be rounded off to the dose of the marketed vials according to the patient's weight. For patients with bone marrow transplant, treatment with sargramostim may be initiated between 1 and 5 days after reinfusion of progenitor cells. It is recommended to reduce the 10 μg/kg/d dose to 5 μg/kg/d once the figure of 100 neutrophils/mm^3 has been reached, and to maintain it until recovery of neutrophils is >1000 cells/mm^3 for at least three days. For GM-CSF, we recommend initiating administration on the day of the reinfusion and maintaining it until recovery of neutrophils is >1500 cells/mm^3 for three consecutive days. The dose may be reduced by 50% when the neutrophil value is >2000 cells/mm^3.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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References

1. Timmer-Bonte JN, de Boo TM, Smit HJ et al (2005) Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. J Clin Oncol 23:7974–7984
2. Vogel CL, Wojtukiewicz MZ, Carroll RR et al (2005) First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 23:1178–1184
3. Bui BN, Chevallier B, Chevreau C et al (1995) Efficacy of lenograstim on hematologic tolerance to MAID chemotherapy in patients with advanced soft tissue sarcoma and consequences on treatment dose-intensity. J Clin Oncol 13:2629–2636
4. Doorduijn JK, van der Holt B, van Imhoff GW et al (2003) CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 21:3041–3050
5. Citron ML, Berry DA, Cirrincione C et al (2003) Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431–1439
6. Chirivella I, Bermejo B, Insa A et al (2009) Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat 114:479–484
7. Pfreundschuh M, Trumper L, Kloess M et al (2004) Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 104:634–641
8. Radosavljevic D, Golubicic I, Gavrilovic D et al (2009) Do the time to chemotherapy response and the dose intensity have an impact on patient outcome in advanced non-small cell lung cancer? J BUON 14:203–209
9. Sarosy GA, Hussain MM, Seiden MV et al (2010) Ten-year follow-up of a phase 2 study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy for poor-prognosis, advanced-stage epithelial ovarian cancer. Cancer 116:1476–1484
10. Lyman GH, Kuderer NM (2004) The economics of the colony-stimulating factors in the prevention and treatment of febrile neutropenia. Crit Rev Oncol Hematol 50:129–146
11. Cosler LE, Eldar-Lissai A, Culakova E et al (2007) Therapeutic use of granulocyte colony-stimulating factors for established febrile neutropenia: effect on costs from a hospital perspective. Pharmacoeconomics 25:343–351
12. Bohlius J, Herbst C, Reiser M et al (2008) Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev (4):CD003189
13. Sung L, Nathan PC, Alibhai SM et al (2007) Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med 147:400–411
14. Kuderer NM, Dale DC, Crawford J, Lyman GH (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25:3158–3167
15. Dale DC, McCarter GC, Crawford J, Lyman GH (2003) Myelotoxicity and dose intensity of chemotherapy: reporting practices from randomized clinical trials. J Natl Compr Canc Netw 1:440–454
16. Clark OA, Lyman GH, Castro AA et al (2005) Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol 23:4198–4214
17. Berghmans T, Paesmans M, Lafitte JJ et al (2002) Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in febrile neutropenic cancer patients. A systematic review of the literature with meta-analysis. Support Care Cancer 10:181–188
18. Garcia-Carbonero R, Mayordomo JI, Tornamira MV et al (2001) Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. J Natl Cancer Inst 93:31–38
19. Saven A, Schwartzberg L, Kaywin P et al (2006) Randomized, double-blind, phase 2 study evaluating same-day vs next-day administration of pegfilgrastim with R-CHOP in non-Hodgkin's lymphoma patients. J Clin Oncol (Meeting Abstract) 24:7570
20. Yardley DA, Burris HA III, Farley CP et al (2008) A phase II feasibility trial of dose-dense docetaxel followed by doxorubicin/cyclophosphamide as adjuvant or neoadjuvant treatment for women with node-positive or high-risk node-negative breast cancer. Clin Breast Cancer 8:242–248
21. Petros WP, Crawford J (1997) Safety of concomitant use of granulocyte-macrophage colony-stimulating factor or granulocyte-macrophage colony-stimulating factor with cytotoxic chemotherapy agents. Curr Opin Hematol 4:213–216
22. Bunn PJ, Crowley J, Kelly K et al (1995) Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of Southwest Oncology Group. J Clin Oncol 13:1632–1641. Erratum in: J Clin Oncol 1995;13:2860
23. Momin F, Kraut M, Lattin P, Valdivieso M (1992) Thrombocytopenia in patients receiving chemoradiotherapy and G-CSF for locally advanced non-small cell lung cancer. Proc Annu Meet Am Soc Clin Oncol 11:983a
24. Morstyn G, Campbell L, Lieschke G et al (1989) Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy. J Clin Oncol 7:1554–1562
25. Ribas A, Albanell J, Bellmunt J et al (1996) Five-day course of granulocyte colony-stimulating factor in patients with prolonged neutropenia after adjuvant chemotherapy for breast cancer is a safe and cost-effective schedule to maintain dose-intensity. J Clin Oncol 14:1573–1580
26. Almenar D, Mayans J, Juan OR et al (2009) Pegfilgrastrim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in spain. Results of the LEARN study. Eur J Cancer Care 18:280–286
27. Von Minckwitz G, Schwenkglenks M, Skacel T et al (2009) Febrile neutropenia and related complications in breast cancer patients receiving pegfilgrastrim primary prophylaxis versus current practice neutropenia management: results from an integrated analysis. Eur J Cancer 45:608–617
28. Marina J, Carabantes FJ, Escrivá de Romani S et al (2009) Current practice of prophylaxis with granulocyte colony-stimulating factors for preventing chemotherapy-induced neutropenia in breast cancer patients in Spain. Eur J Cancer 7[Suppl 1]:181 (abst P-3019)
29. Crawford J, Kreisman H, Garewal H et al (1997) The impact of Filgrastim schedule variation on hematopoietic recovery post-chemotherapy. Ann Oncol 8:1117–1124
30. Koumakis G, Vassilomanolakis M, Barbounis V et al (1999) Optimal timing (Preemptive versus supportive) of granulocyte colony-stimulating factor administration following high-dose cyclophosphamide. Oncology 56:28–35
31. Engert A, del Giglio A, Bias P et al (2009) Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. Onkologie 32:599–604
32. Gascon P, Fuhr U, Sörgel F et al (2010) Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol 21:1419–1429
33. Siena S, Piccart MJ, Holmes FA et al (2003) A combined analysis of two pivotal randomized trials of a single dose of Pegfilgrastrim per chemotherapy cycle and daily Filgrastrim in patients with stage II-IV breast cancer. Oncol Rep 10:715–724
34. Pinto L, Liu Z, Doan Q et al (2007) Comparison of pegfilgrastrim with filgrastrim on febrile neutropenia, grade IV neutropenia and bone pain: meta-analysis of randomized controlled trials. Curr Med Res Opin 23:2283–2295
35. Aapro MS, Bohlius J, Cameron DA et al (2011) 2011 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47:8–32