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Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications

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definition of febrile neutropenia

Febrile neutropenia (FN) is defined as a rise in axillary temperature to >38.5°C for a duration of >1 h while having an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l.

incidence of FN, complication rates and mortality

Despite relatively high rates of low neutrophil count during standard-dose chemotherapy regimens for malignancies other than acute leukaemias, rates of FN, other complication rates and mortality rates are relatively low for most standard chemotherapies (Table 1).

These rates do not justify the systematic use of haematopoietic growth factors (hGFs) such as granulocyte colony-stimulating factor (G-CSF) or its pegylated form (pegfilgrastim) in prophylaxis of chemotherapy-induced neutropenia unless the risk of FN exceeds 20%, or there are special circumstances as outlined below. Colony-stimulating growth factors should be avoided in patients who are not at high risk for FN or neutropenic complications. The use of hGFs for treatment of FN is also not recommended, except in settings with increased morbidity and mortality, including sepsis, tissue infection and prolonged neutropenia. These agents should be particularly avoided in patients with infections not related to neutropenia, such as community- or hospital-acquired pneumonia [I, A].

indication for primary prophylaxis of FN by hGFs

Table 2 describes the indications for primary prophylaxis of FN by hGFs and Table 3 gives examples of chemotherapy regimens with a risk of FN of ∼20%.

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special situations for use of hGFs for standard therapy

Table 4 describes special situations for the use of hGFs for standard therapy.

dose schedule, route of application of G-CSF and pegfilgrastim

Use 5 μg/kg/day of G-CSF subcutaneoulsy (s.c.) 24–72 h after the last day of chemotherapy until sufficient/stable post-nadir ANC recovery (achieving a target ANC of $>10 \times 10^9$/l is not necessary). Pegfilgrastim, injected s.c. as a single dose of either 100 μg/kg (individualized) or of a total dose of 6 mg (general approach), is considered equally effective [I, A].

note

Primary prophylaxis with G-CSF is not indicated during chemoradiotherapy to the chest due to the increased rate of bone marrow suppression associated with an increased risk of complications and death [I, A].

There is also a risk of worsening thrombocytopenia when hGFs are given immediately before or simultaneously with chemotherapy.

There is a possible risk of subsequent acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) in women receiving adjuvant chemotherapy for breast cancer and hGFs. However, this is confounded by the higher doses of chemotherapy received by patients receiving hGFs compared with those receiving standard dose reductions. Long-term follow-up of dose-dense adjuvant chemotherapy where total dose is the same has not demonstrated any difference in leukaemic risk. If an increased risk is confirmed in some settings, the absolute risk is low (1.8% compared with 0.7% within 48 months of breast cancer diagnosis) and, therefore, the benefits of hGFs still outweigh the risk.

use of G-CSF and pegfilgrastim in high-risk situations

Therapy of acute leukaemias, autologous and allogeneic stem cell transplantations (TPLs) lead to higher risks of FN and potentially lethal complications.

Table 1. Incidence of FN

Leukopenia WHO grade 4	2%–28%
Febrile neutropenia	up to 10%–57%
Infection WHO grade 3 or 4	up to 16%
Death in FN	0%–7%

WHO, World Health Organization.

Table 2. Indications for primary prophylaxis of FN by hGFs

Reasonable only if	Parameter
Probability of FN of ~20% based on chemotherapy and/or special situations (see Table 4) or	Affected: ANC recovery [I], fever [I], infection rate [I], use of i.v. antibiotics [II], hospital discharge [I]
Dose reduction deemed detrimental to outcome [A]	Controversial: infectious mortality [I], early mortality
	Not affected: survival [I]

i.v., intravenous.

Table 3. Examples of regimens with a risk of FN of ~20%

Bladder cancer	MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
	TC (paclitaxel, cisplatin)
Breast cancer	TAC (docetaxel, doxorubicin, cyclophosphamide)
	Dose-dense AC/T (doxorubicin, cyclophosphamide, paclitaxel)
Cancer of the cervix	TC (paclitaxel, cisplatin)
Gastric cancer	DCF (docetaxel, cisplatin, fluorouracil)
Head and neck cancer	Paclitaxel, ifosfamide, mesna, cisplatin
Non-Hodgkin lymphoma	CHOP-14
	ICE
	RICE
	DHAP (dexamethasone, cisplatin, cytarabine)
Non-small-cell lung cancer	DP (docetaxel, carboplatin)
Ovarian	Topotecan
Sarcoma	MAID (mesna, doxorubicin, ifosfamide, etoposide)
	Doxorubicin, ifosfamide
Small-cell lung cancer	CAE (cyclophosphamide, doxorubicin, etoposide)
	Topotecan
Testicular cancer	VIP (vinblastine, ifosfamide, cisplatin)

Table 4. Special situations for the use of hGFs for standard therapy

Indication	Special situation	Use of hGF
Primary prophylaxis	Reduced marrow reserve (e.g. ANC $<1.5 \times 10^9$/l) due to radiotherapy of >20% marrow	Yes [III, C]
	Human immunodeficiency virus	Yes [II, B]
	Patients aged ≥65 years treated with curative regimens (CHOP or more intensive regimens for patients with aggressive NHL)	Yes
Secondary prophylaxis	Further infections in the next treatment cycle considered life threatening	Yes
	Dose reduction below threshold	Yes
	Delay of chemotherapy	Yes
	Lack of protocol adherence if compromising cure rate, overall or disease-free survival	Yes
Therapy of afebrile neutropenia	–	No [II, D]
Therapy of FN	General	No [C]
Therapy of high-risk FN	Protracted FN (>7 days), hypotension, sepsis, pneumonia or fungal infection	Yes

NHL, non-Hodgkin's lymphoma.

Incidence of FN in high-risk situations: regular during autologous and allogeneic peripheral blood stem-cell (PBSC) TPLs and bone marrow TPL, during graft failure, in 35%–48% of AML cases at diagnosis and in 13%–30% during acute lymphoblastic leukaemia (ALL) induction chemotherapy.

Mortality: 0%–10% in autologous TPL, highly variable in allogeneic TPL, 80% during graft failure, 20%–26% during the first 2 months in AML and 2%–10% during induction of ALL.

indications for granulopoietic CSFs in high-risk situations

Table 5 describes the indications for granulopoietic CSFs in high-risk situations.

G-CSF after autologous stem-cell TPL

- Marrow TPL: start of hGF. Application may safely be postponed until days 5–7 [I]. The recommended dose of G-CSF is 5 μg/kg daily.
- PBSC TPL: short acceleration of recovery of ANC [I] does not consistently translate into relevant clinical

Table 5. Indications for G-CSFs in high-risk situations

Indication	Use of hGFs	Parameter
Autologous marrow transplant	Yes	ANC [I], fever [I, C], infection [I, C], i.v. antibiotics [I, C] Not affected: infectious mortality [I, A], overall survival [I, A]
Autologous hGF PBSC TPL after reinfusion	Controversial ANC [I]	Not consistently affected: fever, use of i.v. antibiotics Not affected: infectious mortality [I, A], overall survival [I, A]
Allogeneic marrow transplant	Yes	ANC [I, A] Other parameters inconsistent
Graft failure	Yes	Mortality [III–IV, B]
AML	No (trials)	ANC [I, A] Not affected: infectious mortality [I, C], overall survival [I, C]
MDS	No	Mortality may be increased [II, B], despite the absence of an increased transformation to AML
ALL	Controversial	ANC [I, A] Not consistently affected: severe infections, infectious mortality, hospitalization, survival. Increased rates of secondary leukaemia have been reported in childhood ALL treated with G-CSF 6 radiotherapy [III, C]

benefit. In standard-risk patients outside trials are not recommended.

G-CSF after allogeneic TPL

Reasonable after marrow TPL. Clinical benefit restricted to recovery of ANC. Start 5–7 days after TPL is sufficient [I, A]. Insufficient data for TPL with allo-PBSC.

mobilization of PBSCs

autologous PBSC

hGFs ± chemotherapy are effective. The recommended dose of G-CSF is 10 μg/kg daily for 7–10 days before apheresis, with or without chemotherapy. hGF-mobilized PBSCs are superior in terms of recovery of ANC to marrow stem cells plus post-infusion hGFs [I, A].

allogeneic PBSC

Donor convenience, recovery of ANC hastened, no increased rate of acute graft-versus-host disease. Faster ANC recovery after PBSC compared with marrow stem cells. The recommended dose of G-CSF is 10 μg/kg daily for 7–10 days before apheresis, with or without chemotherapy.

special comments on CSFs as a treatment for radiation injury

The use of CSFs as treatment for radiation injury is shown in Table 6.

Table 6. Lethal doses of total body radiotherapy (accidental or intentional)

Indication	Clinical outcome	Use of CSFs
Doses of 3–10 Gy	Probable or certain death from bone marrow failure	Yes
Doses <3 Gy	Survival with excellent nursing care	No
Doses >10 Gy	Death due to injury to other organs such as gastrointestinal tract	No

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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