

Hematopoietic growth factors: ESMO Recommendations for the applications

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definition of febrile neutropenia

Febrile neutropenia (FNP) is defined as a rise in axillary temperature to above 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 FNP, complication rates and mortality

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

These rates do not justify the use of hematopoietic growth factors (hGFs) such as granulocyte colony-stimulating factor (G-CSF) or its pegylated form (pegfilgrastim). Colony-stimulating growth factors should not be used in patients without neutropenia and especially not in patients suffering from community- or hospital-acquired pneumonitis [I, A].

indication for primary prophylaxis of FNP by hGFs

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

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 s.c. 24–72 h after the last day of chemotherapy until sufficient/stable 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

G-CSF is contraindicated during radiotherapy to the chest due to increased rate of complications and death [I, A].

Risk for severe thrombocytopenia when hGFs are given immediately before or simultaneously with chemotherapy.

Possible risk of subsequent acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in women receiving adjuvant chemotherapy for breast cancer and hGFs. Even if these results will be confirmed, the absolute risk is low (1.8% versus 0.7%

Table 1.

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

FNP, febrile neutropenia; WHO, World Health Organization.

Table 2. Indications for primary prophylaxis of FNP by hGFs

Reasonable only if	Parameter
Probability of FNP ~20% or	<i>Affected:</i> ANC recovery [I], fever [I], infection rate [I], use of i.v. antibiotics [II], hospital discharge [I]
Dose reduction deemed detrimental to outcome [A]	<i>Controversial:</i> infectious mortality [I]
	<i>Not affected:</i> Survival [I]

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Approved by the ESMO Guidelines Working Group: February 2002, last update February 2008. This publication supercedes the previously published version—Ann Oncol 2007; 18 (Suppl 2): ii89–ii91.

Conflict of interest: the authors have reported no conflicts of interest.

Table 3. Examples of regimens with a risk of FNP 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's 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 non-Hodgkin lymphoma)	Yes
Secondary prophylaxis	Further infections in the next treatment cycle considered life threatening	Yes
	Dose reduction below threshold Delay of chemotherapy Lack of protocol adherence if compromising cure rate, overall or disease-free survival	
Therapy of afebrile neutropenia	–	No [II, D]
Therapy of FNP	General	No [C]
Therapy of high-risk FNP	Protracted FNP (>7 days), hypotension, sepsis, pneumonia or fungal infection	Yes

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 leukemias, autologous and allogeneic stem cell transplantations (TPLs) lead to higher risks of FNP and potentially lethal complications.

Incidence of FNP 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 leukemia (ALL) induction chemotherapy.

Mortality: 0–10% in autologous TPL, highly variable in allogeneic TPL, 80% during graft failure, 20–26% during 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 day 5–7 [I]. Recommended dose of G-CSF is 5 $\mu\text{g}/\text{kg}$.

PBSC TPL: short acceleration of recovery of ANC [I] does not consistently translate into relevant clinical 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 sufficient [I, A]. Insufficient data for TPL with allo-PBSC.

mobilization of peripheral blood stem cells (PBSC)

autologous PBSC

HGFs \pm chemotherapy are effective. The recommended dose of G-CSF is 10 $\mu\text{g}/\text{kg}$. hGF-mobilized PBSCs are superior in terms of recovery of ANC over marrow stem cells plus postinfusion 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 versus marrow stem cells.

special comments on CSFs as a treatment for radiation injury

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

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

Indication	Use of hGFs	Parameter
Autologous marrow transplant	Yes	ANC [I], fever [I, C], infection [I, C], intravenous 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 leukemia have been reported in childhood ALL treated with G-CSF ± radiotherapy [III, C]
Indication	Clinical outcome	Use of CSFs
Doses of 3–10 Gy	Probable or certain death from BM 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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