BSMO Management of febrile neutropenia (FN) guidelines

Based on ESMO guidelines (1)

1. Primary prophylaxis of FN with G-CSF (Granulocyte-Colony Stimulating Factors)

1.1 ESMO recommendations

1.1.1 Primary prophylaxis: modalities

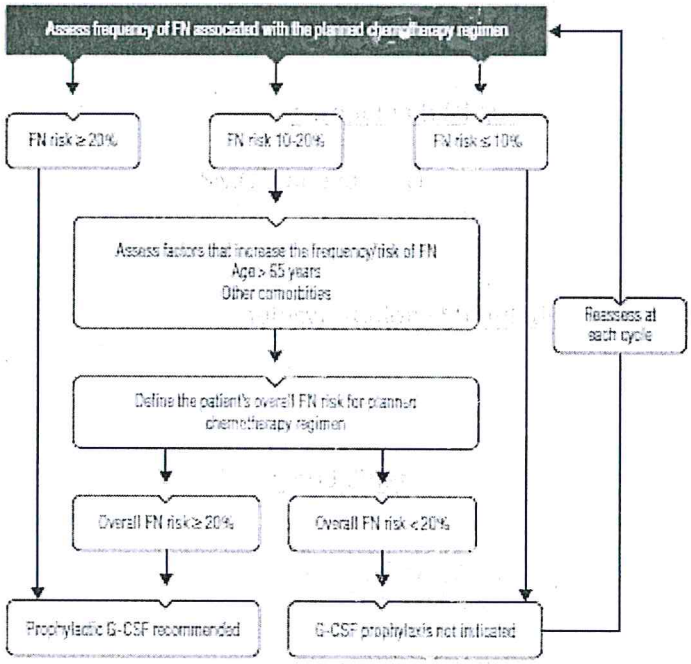

Figure 1. Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage, adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropenia ; G-CSF, granulocyte colony-stimulating factor. Reprinted from (2), with permission from Elsevier.

Most guidelines recommend that G-CSF be administered prophylactically if the risk of FN is >20% for all planned cycles of treatment. Classifications of the risk according to the type of chemotherapy (CT) have been published and updated (2). For patients with an intermediate risk (10-20%), it is important to consider the patients' age and particularly any coexisting morbidities (2-4). An algorithm for the decisions about primary prophylactic G-CSF use is presented in Figure 1.

Beside this approach, G-CSF can be considered in patients with reduced bone marrow reserve due to extensive radiotherapy or patients who are neutropenic in the context of HIV infection.

With most CT used for the treatment of common tumours, the risk of FN is maximal during this first course ; thus, it makes sense to recommend primary prophylaxis for the patients at risk rather than to systematically resort to secondary prophylaxis.
Secondary prophylaxis (i.e. G-CSF given for a course of CT following a course with FN) is indicated if dose reduction or delay of CT is not desirable (e.g. treatment with a curative intent).
There are few complications associated with G-CSF administration ; the most common adverse effect is minor or moderate bone pain that can usually be handled with standard analgesics.

1.1.2. Dose schedule, route of application of G-CSF and pegfilgrastim

Use 5 µg/kg/day of G-CSF subcutaneously (s.c.) 24-72 h after the last day of CT until sufficient/stable post-nadir ANC recovery (achieving a target ANC of >10-10^9/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. The equivalent dose of filgrastim is 5 µg/kg/day for ≈ 10 days. There are no adequate data for reduced numbers or days or alternate days of G-CSF instead of standard, neither for use on day 1 instead of on day 2. EMA/FDA approved biosimilars can be considered (i.e. lipegfilgrastim).

1.1.3. Use of G-CSF in high-risk situations

The therapy of acute leukemias, autologous and allogeneic stem cell transplantations (TPLs) leads to higher risks of FN and potentially lethal complications (5).

1.2. Recommendations in Belgium

Basically, for pegfilgrastim (Neulasta®) and lipegfilgrastim (Lonquex®), the ESMO recommendations are applicable in Belgium and will allow the reimbursement of the medications (a valid prescription is required).

Thus, in summary,

1.2.1 Primary prohylaxis with a long-acting G-CSF is reimbursed by the social security system for

- CT with a risk of FN ≥20%
- CT with a risk of FN ≥10% provided the presence of additional risk factors linked to the patient or to the tumor
- in case of dose-dense or dose-intense CT schedules
- to prevent CT reduction and/or delay, especially for treatments with curative intent or first-line therapy for metastatic disease

1.2.2. Secondary prophylaxis (during or after CT) in case of
- neutropenia < 500/cumm and fever >38°C
- neutropenia < 500/cumm lasting at least 5 days

Important caveat : the reimbursement of short-acting G-CSF's (filgrastim, tevagrastim, and others) is still regulated in Belgium by cumbersome rules that take into account the tumor type and, to some extent, the type of CT and age ; the recommendations do not correspond to ESMO (and other international) regulations and should not be followed.
Moreover, because the use of short-acting G-CSF's is overall more complicated and possibly less effective (6) than that of long-acting preparations, we recommend to limit the prescription of short-acting G-CSF's to rare situations where a prompt but time-limited stimulation of the granulopoietic function is indicated.

2. Management of FN (ESMO guidelines that can be endorsed by BSMO)

2.1. General principles

Success in FN management requires prompt recognition of, and reaction to, potential infection. It is vital to educate outpatients to monitor their symptoms, including body temperature, and to contact the appropriate service in the event of concerns. The first administration of therapy should be given in the hospital within 1h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

However, the spectrum of infection in cancer patients is different according to places and changes over time ; therefore, paying attention to local epidemiology is crucial (7). The vast majority of FN cases, as managed according to the algorithm set out in Figure 2, respond promptly to empirical therapy, suffering no major complications. A number of instruments have been developed in attempts to predict these low-risk cases where complications are not likely. The most widely used instrument, the MASCC index, allows the clinician to rapidly assess, on just a clinical basis, the risk of a patient with FN. The MASCC score has been prospectively validated in several studies. The criteria and weighting scores are listed in Table 1. Low-risk cases are those scoring ≥21. The serious medical complication rate in low-risk cases is estimated to be 6% and the mortality rate to be below 1%. If an obvious focus on infection is apparent, antibacterials should be tailored accordingly.

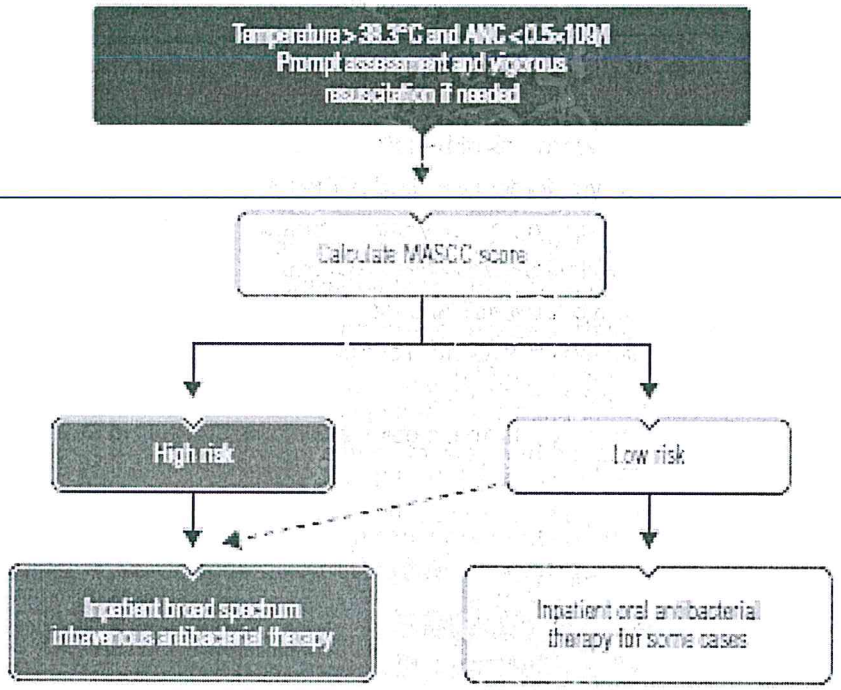

Figure 2. Initial management of febrile neutropenia. ANC, absolute neutrophil count ; MASCC, Multinational Association of Supportive Care in Cancer.

Table 1. MASCC febrile neutropaenia risk index

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with scores ≥21 are at low risk of complications. Points attributed to the variable « burden of illness » are not cumulative. The maximum theoretical score is therefore 26 (8). Reprinted with permission. © 2000 American Society of Clinical Oncology. All rights reserved.
BP, blood pressure.

2.2. Low-risk patients

A recent review has concluded that oral antibacterial therapy can be safely substituted for conventional intravenous (i.v.) treatment in some low-risk FN patients, namely those who are hemodynamically stable and do not present clinical signs of infection.

Single-agent quinolones (moxifloxacin) were not inferior to combinations (quinolone with amoxycillin plus clavulanic acid). Oral quinolone therapy should not be used in patients who have taken a quinolone antibacterial as prophylaxis.

The possibility of oral outpatient management for low-risk FN cases has become increasingly appealing (9). Early discharge can be considered in these low-risk cases once they have become clinically stable, symptomatically better with evidence of fever lysis after a minimum of 24h in hospital, and provided that there is an adequate understanding of the risks and that patient surveillance is available (10-13).

2.3. High-risk patients

Patients with FN who are at high risk, as assessed by the MASCC criteria (<21), or have high-risk features as clinically judged, should be admitted and commenced on broad-spectrum i.v. antibiotics, since the risk of bacterial sepsis is high (14).
Local epidemiological bacterial isolate and resistance patterns are crucially important in determining the first-choice empirical therapy, since coverage for MRSA or resistant Gram-negative bacteria may be required (15). A meta-analysis comparing monotherapy (e.g. an anti- pseudomonal cephalosporin like ceftazidime or cefepime, imipenem, meropenem or piperacillin-tazobactam) with combination therapy including an aminoglycoside found equivalent efficacy (16, 17). This is less clear in the subsets at high risk of prolonged neutropenia and those with bacteraemia, where the bactericidal activity and synergistic effect of a β-lactam antibiotic in combination with an aminoglycoside might be preferable ; namely, in case of *Pseudomonas aeruginosa* sepsis or in centres with known intermediate susceptibility of Gram-negative bacilli to β-lactams (18).

The frequency of clinical assessment is determined by clinical severity but may be required every 2-4h in cases needing resuscitation. Daily assessment of fever trends, bone marrow and renal function is indicated until the patient is afebrile and has an ANC of $\geq 0.5 \times 10^9$/l for 24h. Repeated imaging may be required in patients with persistent pyrexia. A consultation with an expert in infectious diseases is highly recommended, especially in patients with persistent fever, who might require anti-fungal therapy.

If the patient is afebrile and has an ANC of $\geq 0.5 \times 10^9$/l at 48h, and no cause of infection has been found, consider changing to oral antibiotics ; if the patient is on dual therapy, aminoglycoside may be discontinued.

2.4. Duration of therapy

If the ANC is ≥0.5 x 10^9/l, the patient is asymptomatic and has been afebrile for 48h and blood cultures are negative, antibacterials can be discontinued.
If the ANC is ≤0.5 x 10^9/l, the patient has suffered no complications and has been afebrile for 5-7 days, antibacterials can be discontinued except in certain high-risk situations such as patients with acute leukemia and/or following high-dose CT, when antibacterials are often continued for up to 10 days, or until the ANC is ≥0.5 x 10^9/l.

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