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Review

The impact of new European Organisation for Research and Treatment of Cancer guidelines on the use of granulocyte colony-stimulating factor on the management of breast cancer patients

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ABSTRACT

Febrile neutropenia (FN) is a severe consequence of myelosuppressive therapy. The European Organisation for Research and Treatment of Cancer recently published guidelines on the use of granulocyte colony-stimulating factor (G-CSF) to prevent FN in patients with malignant disease. In this review, the impact of these guidelines on breast cancer treatment is discussed. A brief summary of FN in breast cancer is given, and patient-related and treatment schedule-related risk factors for FN are reviewed for the adjuvant/neoadjuvant and metastatic disease settings. Primary G-CSF support is recommended if the overall FN risk is $\geqslant$20%, or if a reduction in dose-intensity is associated with a poorer outcome. Any formulation of G-CSF is recommended. The utility of G-CSF in reducing the incidence of FN and enabling treatment regimens is discussed.

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1. Introduction

Myelosuppression is an almost inevitable result of treatment with many of the cytotoxic agents that are effective for breast cancer and may lead to a number of complications including neutropenia, anaemia and thrombocytopenia. However, thrombocytopenia is uncommon in the management of breast cancer, while anaemia is generally easily managed.[1] In contrast, severe (Grade 4) neutropenia and febrile neutropenia (FN) are therefore the most frequent serious sequelae of myelosuppression in breast cancer patients and tend to present during the initial cycles of chemotherapy.[2–5] FN is strongly linked to mortality because of the risk of life-threatening infection.[2–4] Physicians may therefore limit chemotherapy dosing from the outset in an attempt to avoid neutropenia; alternatively, they may interrupt, reduce or withdraw treatment if it occurs. All of these approaches potentially compromise chemotherapy dose intensity with negative consequences for patient outcome.[2,4–8]

FN needs to be treated as a medical emergency. Often requiring hospitalisation with intravenous anti-infective treatment, the direct and indirect costs of FN to healthcare providers and patients are high.[2,3,5,9] In a recent retrospective chart review study from Spain, it was estimated that each FN episode costs €3519 to manage.[9]

Colony-stimulating factors (CSFs) are the only biological response modifiers currently available to prevent severe neutropenia and FN.[3] Granulocyte-CSFs (G-CSF), including filgrastim, lenograstim and the long-acting pegfilgrastim, are most frequently used in clinical practice.[4] A recent meta-analysis of 17 randomised clinical trials including 3493 patients demonstrated that prophylactic G-CSF reduced the risk of FN and early deaths (including infection-related mortality) in adult cancer patients receiving chemotherapy.[10] In 2006, the European Organisation for Research and Treatment of Cancer (EORTC) published new European-focused guidelines on the use of G-CSF in malignant disease. Following closely behind similar guidance from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN),[11,12] these guidelines are based upon a systematic review of clinical evidence and represent a significant advance in the management of chemotherapy-induced neutropenia. The purpose of this review is to discuss the importance of the EORTC recommendations in the specific context of breast cancer treatment in Europe. In the following sections, patient-related risk factors for FN are discussed, followed by regimen-related FN risk factors and treatment intent by setting, indicating how these new recommendations can change clinical practice.

2. EORTC guidelines for the use of G-CSFs to manage chemotherapy-induced neutropenia

Key recommendations from the EORTC guidelines are shown in Fig. 1.[4] Importantly, it is now recommended that primary prophylaxis with G-CSF should be given from the first cycle if the overall risk of FN from chemotherapy- and patient-related factors is $\geqslant$20%. When the treatment-associated risk of FN is 10–20%, patient-related risk factors should be assessed to determine whether the overall risk is $\geqslant$20%, in which case, primary prophylactic G-CSF would be indicated. Patients receiving treatment regimens with FN risk <10% should not normally require G-CSF primary prophylaxis.[4] This guidance is summarised in the treatment algorithm shown in Fig. 2.

The EORTC recommendations are evidence-based, and represent a consensus within the oncology community, closely mirroring recent guidelines provided by ASCO and NCCN.[11,12] In the previous ASCO guidelines, G-CSF prophylaxis was recommended only when the overall FN risk was >40%.[13] On the basis of recent data demonstrating the benefits of G-CSF, all three organisations now advocate lowering the threshold for growth factor primary prophylaxis to FN risk $\geqslant$20%.

Treatment outcome in patients with breast cancer correlates well with the dose intensity of chemotherapy.[14] Complications resulting from myelosuppression, including FN, may delay treatment or force dose reductions, thereby reducing the dose intensity and efficacy of chemotherapy.[8] Primary prophylactic administration of G-CSF may enable scheduled chemotherapy regimens to be delivered while reducing the toxic burden on the patient. The EORTC guidelines recommend that G-CSF prophylaxis should be prescribed if chemotherapy dose-reduction or treatment interruption is associated with a poorer prognosis (Fig. 1). Furthermore, the EORTC guidelines state that if dose-intense or dose-dense chemotherapy regimens have survival benefits, G-CSF prophylaxis should be used, regardless of patient-related risk factors for FN (Fig. 1). Thus, given that adjuvant chemotherapy for patients with early breast cancer is given to increase the chance of cure, G-CSF use is strongly recommended whenever using a dose-intensive regimen.[4] Dose-dense and dose-intense chemotherapies are being used in Europe as physicians endeavour to improve clinical outcomes. However, these regimens are still to be widely adopted in clinical practice and are mainly employed within the framework of clinical trials.

3. Patient-related risk factors for FN

Patient-related risk factors that are likely to increase the overall risk of FN include age $\geqslant$65 years, advanced stage of the disease and previous experience of FN.[4,15]

Poor performance status, poor nutritional status, female gender, anaemia, liver disease, renal disease and cardiovascular disease are other parameters proposed as risk factors for FN. However, they were supported only by low-level evidence.[4]

4. Treatment-related risk factors for FN

Chemotherapy regimens differ widely in their associated FN risks. Tables 1–4[4,16–69] detail the FN risk for frequently used regimens in a number of breast cancer settings: adjuvant and neoadjuvant treatment of early stage breast cancer, as well as first- and second-line treatment of metastatic disease. The lists of regimens in these tables are not exhaustive. Wherever possible, data are presented for regimens given without G-CSF support. For those regimens in which data

Recommendation 1: patient-related risk factors for FN should be evaluated before administering each chemotherapy cycle. These include age ≥65 years, advanced stage of disease, previous history of FN, lack of G-CSF use, and lack of antibiotic prophylaxis. Indiscriminate use of antibiotics, however, is not recommended.

Recommendation 2: the elevated risk of FN when using certain chemotherapy regimens should be considered.

Recommendation 3: if reductions in dose intensity or density are known to be associated with a poor prognosis, or when dose-dense or –intense chemotherapy regimens have survival benefits, prophylactic G-CSF should be prescribed. Where this is not crucial, use of less myelosuppressive therapy or dose/schedule modification should be considered.

Recommendation 4: the risk of FN should be assessed for each patient, taking into account patient-related (recommendation 1) and regimen-related (recommendation 2) risk factors, and treatment intent (recommendation 3). If the patient is at ≥20% overall risk of FN, prophylactic G-CSF is recommended. When using chemotherapy regimens with a FN risk of 10–20%, attention should be given to patient characteristics that may increase the overall risk of FN.

Recommendation 5: treatment with G-CSF should be considered for patients with ongoing FN who do not respond to expert antibiotic management.

Recommendation 6: filgrastim, lenograstim and pegfilgrastim are efficacious and there are few clinical differences between these agents. Any is recommended. Additional efficacy may be achieved with pegfilgrastim, but this requires further clarification.

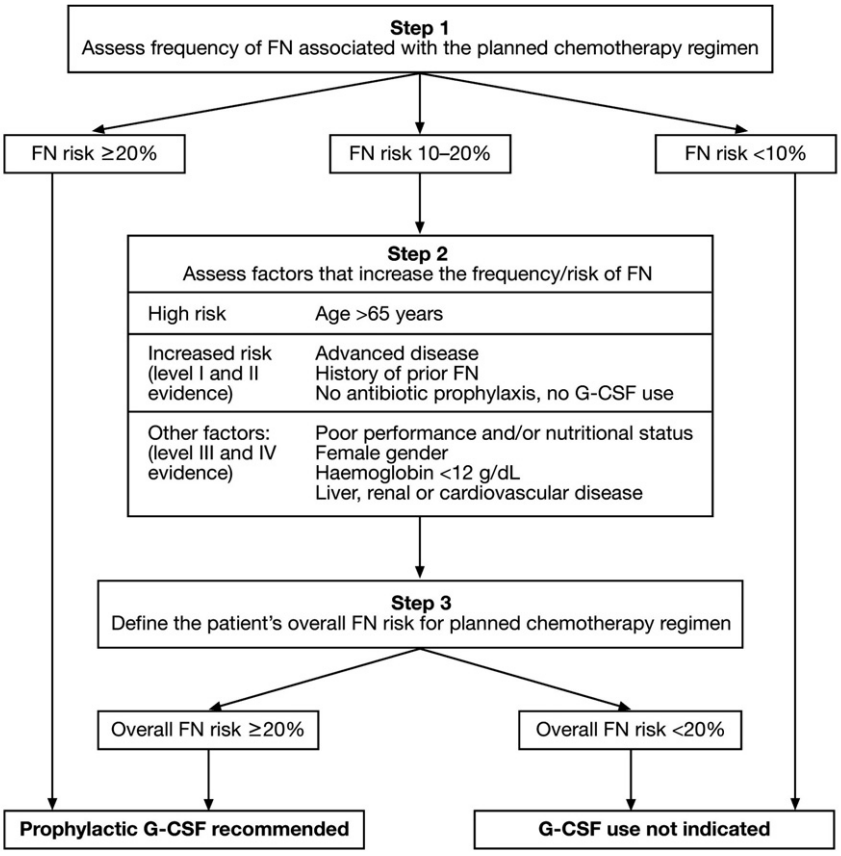
FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor

Fig. 1 – Key EORTC recommendations for the use of G-CSF in cancer.[4]

are only available with G-CSF (e.g. dose-dense), it is a reasonable assumption that FN rates would be higher in the absence of growth factor. It is also evident that some chemotherapy drugs, for example docetaxel, are generally associated with higher FN rates than others. Consequently, FN is relatively infrequent with some standard regimens such as fluorouracil, epirubicin and cyclophosphamide (FEC), but much more common with regimens such as docetaxel, doxorubicin and cyclophosphamide (TAC).

As previously mentioned, treatment intent and treatment schedule should be taken into account when assessing FN risk. If the treatment intent is curative (as in the adjuvant and neoadjuvant settings), maintaining the planned dose density and/or intensity of chemotherapy is of high priority, but this approach can be associated with high attendant risk of FN. Conversely, if treatment is of palliative intent (e.g. in metastatic breast cancer [MBC]), maintaining the planned dose density is less critical, and myelosuppression can be avoided to some extent by dose adjustment. Furthermore, reducing hospitalisation by avoiding FN may be of further benefit to patients in this setting.

Lack of antibiotic prophylaxis is also listed by the EORTC guidelines as a risk factor for FN. Appropriate use of prophylactic antibiotics in patients with malignant disease may reduce the incidence of FN and associated mortality.[70–72] However, the indiscriminate use of antibiotics is not recommended because of the potential development of resistant strains of bacteria.[4] Recently, a meta-analysis assessed the effect of quinolone prophylaxis following chemotherapy on the emergence of resistant bacteria in neutropenic patients.[73] The results showed that there was no statistically significant increase in colonisation by quinolone-resistant bacteria.



FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor

Reproduced from Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006;42;2433–53, with permission from Elsevier.

Fig. 2 – Patient assessment algorithm for the targeting of prophylactic G-CSF treatment.[4]

Thus, authors concluded that the potential benefits of antibiotic prophylaxis (e.g. reduction in the risk of death) outweighed the risk of developing resistance.[73] With these latest data in mind, there are small risk groups in which prophylactic antibiotic use is thought to be advantageous. For example, those patients suffering from lymphoedema-associated cellulitis (erysipelas) or those patients with immediate breast reconstruction following early breast cancer, who are at a higher risk of developing clinically overt infection during adjuvant chemotherapy. Appropriate antibiotic support should also be given to patients with previous history of FN or documented infections, despite prophylactic G-CSF treatment, especially if they are being treated with curative intent.

Finally, patients' FN risk may be influenced by treatments administered concomitantly with chemotherapy. For example, FN risk is likely to be increased by the use of concomitant radiotherapy. This aspect of treatment does not form part of the EORTC guidelines, however, and is outside the scope of this review. Chemotherapy is also being combined with biological agents on an increasingly regular basis. In particular, its combination with trastuzumab, a humanised monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2), has proved efficacious in the treatment of HER2-positive MBC.[74] The impact of trastuzumab on myelosuppression is specifically discussed in a subsequent section on the treatment of MBC.

5. Quantifying FN risk

Chemotherapy regimens are associated with a specific risk of FN that informs the use of G-CSF prophylaxis, but quantifying the additional FN risk conferred by patient-related factors is more problematic. Accordingly, there is much interest in the development of scoring systems to aid evaluation of overall FN risk.[8,75,76] Once refined and validated, such tools promise to become increasingly important in the appropriate targeting of patients for G-CSF prophylaxis.

6. The use of G-CSF during adjuvant and neoadjuvant treatment of early-stage breast cancer

6.1. *Treatment intent*

A large retrospective study in breast cancer patients has shown that dose delays or reductions in adjuvant chemother-

Table 1 – Treatment regimens commonly used for breast cancer in Europe and their associated risks of FN: adjuvant setting[a]

Chemotherapy regimen	References	Dose (mg/m^2 unless otherwise indicated)	Risk of grade 3 and grade 4 neutropenia (%)	Risk of FN (%)	DFS rate (%)	OS rate (%)	Level of evidence
FN risk >20%							
ET (T = doc)	Spielmann[16] (*n* = 1492)	75/75 Q3W	–	31	–	–	I
TAC (T = doc)	Martin[17] (*n* = 745); Martin[18] (*n* = 539)	75/50/500 Q3W	66	25	5Y: 75	5Y: 87	I
FN risk 10–20%							
FEC → T (T = doc)	Roché[19] (*n* = 1001)	500/100/500 → 100 Q3W	–	11	5Y: 78	5Y: 91	I
T → EC (T = doc)	Lopez[20] (*n* = 376)	100 → 120/600 Q3W	–	10	–	–	I
FEC 100	French Adjuvant Study Group[21](*n* = 276); Roché[19] (*n* = 996); Spielmann[16] (*n* = 1518)	500/100/500 Q3W	25	3–10	5Y: 66–73	5Y: 77–87	I
FN risk <10%							
EC	Lopez[20] (*n* = 374)	120/600 Q3W	82	4–7	5Y: 73	5Y: 80	I
AC → T (T = pac)	Citron[22] (*n* = 501)	60/600 → 175 Q3W	43	5[b]	4Y: 75	3Y: 90	I
TC (T = doc)	Jones[23] (*n* = 506)	75/600 Q3W	–	5	5Y: 86	5Y: 90	I
AC[c]	Fumoleau[24] (*n* = 74); Jones[23] (*n* = 510)	60/600 Q3W	–	2–3	5Y: 41–80	5Y: 61–87	I
Oral CMF	Levine[25] (*n* = 359)	$100^{d1-14}/40^{d1+8}/600^{d1+8}$ Q4W	–	1	5Y: 53	5Y: 70	I
CMF	Ron[26] (*n* = 77)	600/40/600 Q3W	–	0	–	–	I
Dose-dense regimens							
DD AC → T (T = pac) + G-CSF	Citron[22] (*n* = 495)	60/600 → 175 Q2W + G-CSF	9	2[b]	4Y: 82	3Y: 92	I

A = doxorubicin; AUC = area under the curve; C = cyclophosphamide; carb = carboplatin; cis = cisplatin; DD = dose-dense; DFS = disease-free survival; DI = dose-intense; doc = docetaxel; E = epirubicin; epidox = epidoxorubicin; F = 5-fluorouracil; FN = febrile neutropenia; G = gemcitabine; G-CSF = granulocyte colony-stimulating factor; H = trastuzumab; LV = leucovorin; M = methotrexate; pac = paclitaxel; X = capecitabine; OR = overall response; OS = overall survival; pCR = pathological complete response; PFS = progression-free survival; vino = vinorelbine; Y = year. Drugs are given on Day 1 of a cycle unless otherwise indicated.

Level of evidence: I = evidence obtained from high-power randomised, controlled clinical trial; II = evidence obtained from at least one well-designed experimental study or low-power randomised, controlled clinical trial; III = evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time or matched case–control series.[4]

Wherever possible, data are presented for regimens given without G-CSF support. For those regimens in which data are only available with G-CSF, it is reasonable to assume that FN rates would be much higher in the absence of growth factor.

a The list of regimens in this table is not exhaustive.

b Data only available for FN that led to hospitalisation.

c The EORTC guidelines note that AC has a FN risk of 10–20%[4] based on the NCCN analysis;[27] although the former acknowledge that some clinicians consider AC to be a low-risk regimen.

apy dose intensity are negatively correlated with disease-free survival (DFS) and overall survival (OS).[7] In practice, therefore, when chemotherapy is given to increase the chance of cure, the aim is to maintain high relative dose intensity (RDI) (>85%). However, because many patients given adjuvant chemotherapy do not actually need it, since they are already cured, the risks of chemotherapy must be balanced against the benefits. Physicians must therefore be vigilant regarding the risk:benefit ratio of such treatment in individual patients and avoid causing undue harm.

Appropriate use of prophylactic G-CSF both assists the maintenance of high RDI, by reducing FN-related dose modification, and reduces the potential harm of myelosuppressive regimens.

6.2. *Patient-related risk factors for FN*

In the adjuvant/neoadjuvant settings, the most relevant patient-related risk factor is advanced age.[4] Even in younger patients, however, there is still a risk of severe neutropenia and FN from a myelosuppressive regimen (see below).

6.3. *Regimen-related risk factors for FN*

A prospective, observational, multinational European study has recently provided an overview of breast cancer therapies in the adjuvant/neoadjuvant settings over the period 2004–2005.[77] Data for 305 patients were collected. Most patients (81%) received anthracycline-based or cyclophosphamide,

Table 2 – Treatment regimens commonly used for breast cancer in Europe and their associated risk of FN: neoadjuvant setting[a]

Chemotherapy regimen	References	Dose (mg/m^2 unless otherwise indicated)	Risk of grade 3–4 neutropenia (%)	Risk of FN (%)	Response rates (%)	Level of evidence
FN risk 10–20%						
TH (T = doc)	Coudert[28] (n = 33)	100 Q3W + 2–4 mg/kg Q1W	85	18	OR 96 pCR 73	III
FN risk <10%						
GT/liposomal A (T = doc) + G-CSF	Schmid[29] (n = 44)	350^{d4}/75/60 Q3W + G-CSF	61	3	OR 80 pCR 25	III
AC → T (T = pac)	Ellis[30] (n = 133)	60/600 Q3W → 80 Q1W	47	2	pCR 17	I
T/cis/H (T = doc) + G-CSF	Hurley[31] (n = 48)	70/70 Q3W + 2–4 mg/kg Q1W + G-CSF	–	0	OR 100 pCR 46	III
Dose-dense regimens						
DD AC → T (T = pac) + G-CSF	Ellis[30] (n = 132)	24/60$^{d1–7}$ Q1W → 80 Q1W + G-CSF	16	1	pCR 27	I

a The list of regimens in this table is not exhaustive.

methotrexate, 5-fluorouracil (CMF) chemotherapies, which have a low risk of FN (⩽10%). The remainder received anthracycline plus taxane-based therapy. Although severe neutropenia was experienced by 41% of patients, FN was observed in just 5%. However, over a quarter (27%) of patients who developed FN, ultimately, received less chemotherapy than is ideal, with an RDI ⩽85%.[77]

Whilst anthracycline regimens are a mainstay of treatment in Europe, additional use of taxanes is increasing. For example, the TAC regimen is considered one of the standards of care in adjuvant treatment of breast cancer, being associated with a 5-year OS rate of almost 90%,[17] although, this regimen is associated with a risk of FN around 25% (Table 1). Therefore, guidelines recommend that G-CSF prophylaxis be given to all patients treated with this regimen from the first cycle. This approach has been confirmed to substantially reduce the risk of FN to 6% or 7%.[17,18,78]

FEC is a frequently used anthracycline regimen in Europe and up to 10% of patients receiving high-dose FEC100 chemotherapy may experience FN.[16,19,21] According to the EORTC guidelines, this is an insufficient risk to automatically warrant primary prophylaxis with G-CSF, but patient factors such as age may increase FN risk. Overall risk should be assessed before every cycle of chemotherapy, and if that risk is perceived to be ⩾20%, then G-CSF prophylaxis should be implemented.[4]

EORTC guidelines do not advocate the use of prophylactic G-CSF with regimens that have a FN risk of <10%.[4] This category includes adjuvant EC,[20,50] CMF,[25,26] docetaxel and cyclophosphamide (TC),[23] and AC.[23]

As previously explained, the use of dose-intense and dose-dense chemotherapies has implications for FN risk, both in terms of higher dosing and shorter dosing intervals. G-CSF primary prophylaxis is mandatory to prevent severe neutropenia and/or FN such that curative dosing levels can be maintained. For example, adjuvant administration of accelerated EC followed by high-dose EC/thiotepa to patients (n = 201) with extensive axillary lymph node involvement[79] was associated with a significantly higher OS rate at 4 years (75%) than a corresponding regimen consisting of accelerated EC, followed by dose-dense CMF (70%). However, even with G-CSF support, FN was far more frequent in the first regimen versus the second regimen (70% versus 2%).

In the neoadjuvant setting (total number of evaluable patients = 265), dose-dense AC followed by paclitaxel, with G-CSF support, was more efficacious than the corresponding 3-weekly conventional regimen (pathological complete response: 27% versus 17%, respectively, p = 0.06). With G-CSF support, the risk of FN was low for both regimens (1% versus 2%)[30] (Table 2). Similarly, in the adjuvant setting, a dose-dense, 2-weekly regimen of high-dose E followed by C and then paclitaxel, plus G-CSF support, was compared with a conventional 3-weekly regimen of EC followed by paclitaxel.[80] Here, dose-intensive treatment achieved a greater DFS (80% versus 70%, p = 0.03; 95% CI: 0.44–0.96) rate at 3 years, with only a marginally increased incidence of FN (7% versus 2%, respectively). Although it should be noted that after a longer follow-up period of 69 months the difference in OS was not significant.[81] These findings reflect data for adjuvant dose-dense AC followed by paclitaxel, again given with G-CSF support. For this regimen, the FN hospitalisation rate was just 2%, with a 3-year OS of 92%.[22]

7. G-CSF use during the treatment of MBC

7.1. *Treatment intent*

Patients with MBC have a poor prognosis. Accordingly, treatment is directed towards prolonging life and/or palliation of disease-related symptoms rather than towards cure, although complete remissions are occasionally observed. Physicians must balance treatment to prolong life and improve the quality of life without undue toxicity (e.g. excessive myelosuppression).[82] Consequently, the maintenance of high dose intensity is not necessarily a high priority for patients with MBC. Indeed, the EORTC guidelines suggest that if maintenance of dose intensity is not crucial, the use of less myelosuppressive chemotherapies or dose schedules could be

Table 3 – Treatment regimens commonly used for the treatment of breast cancer in Europe and their associated risk of FN: first-line therapy for metastatic disease (excluding prior adjuvant/neoadjuvant treatment)[a]

Chemotherapy regimen	References	Dose (mg/m^2 unless otherwise indicated)	Risk of grade 3–4 neutropenia (%)	Risk of FN (%)	Response rates (%)	Median survival (months)	Level of evidence
FN risk >20%							
AT (T = doc)	Nabholtz[32] (*n* = 214); Alba[33] (*n* = 69)	50/75 Q3W	13–97	33–48	OR 51 pCR 6	OS 22–23	I
T → AC (T = doc)	Perez[34] (*n* = 17)	100 → 60/600 Q3W	100	40	OR 35 pCR 6	OS 30 PFS 12	II
AT (T = pac)	Biganzoli[35] (*n* = 138)	60/175 Q3W	89[b]	32	OR 58 pCR 7	OS 21 PFS 6	I
A → T (T = doc)	Alba[33] (*n* = 75)	75 Q3W → 100 Q3W	11	29	OR 61 pCR 12	OS 22	I
FN risk 10–20%							
GAT (T = pac)	Passardi[36] (*n* = 33)	800^{d6}/50/160^{d2} Q3–4	69	18	OR 55 pCR 7	OS 36 PFS 10	III
T/carb/H (T = doc)	Pegram[37] (*n* = 62)	75/6 AUC Q3W + 2–4 mg/kg Q1W	65[b]	16	OR 58 pCR 20	PFS 13	II
T/cis/H (T = doc)	Pegram[37] (*n* = 62)	75/75 Q3W + 2–4 mg/kg Q1W	16[b]	13	OR 79 pCR 5	PFS 10	II
GET (T = pac)	Zielinski[38] (*n* = 124)	1000^{d1+4}/90^{d1}/175 Q3W	93	12	OR 63 pCR 10	OS 30 PFS 9	I
AC	Biganzoli[35] (*n* = 135); Nabholtz[32] (*n* = 215)	60/600 Q3W	81–88[b]	9–10	OR 47–54 pCR 3–7	OS 21–22 PFS 6	I
FN risk <10%							
AT (T = pac)	Jassem[39] (*n* = 134)	50/220 Q3W	89	8	OR 68 pCR 19	OS 23 PFS 8	I
TG (T = pac)	Albain[40] (*n* = 267)	175/1250^{d1+8} Q3W	48	5	OR 41	OS 19 PFS 5	I
Vino/X	Ghosn[41] (*n* = 30)	25^{d1+8}/1650^{d1-14} Q3W	7	7	OR 70 pCR 7	OS 30 PFS 10	III
TAC (T = doc) + G-CSF	Nabholtz[42] (*n* = 413)	75/50/500 Q3W + G-CSF	85[b]	7[c]	–	–	I
Vino	Freyer[43] (*n* = 58)	60–80	39	5	OR 31 CR 7	PFS 4	III
G/cis	Fuentes[44] (*n* = 46)	1200–1250^{d1+8}/75^{d1}	41	4	OR 81 pCR 17	OS 28 PFS 15	III
Weekly T (T = pac)	ten Tije[45] (*n* = 23); Gasparini[46] (*n* = 62)	80$^{d1,8+15}$ Q4W or Q1W	7–12	2–4	OR 38–57 pCR 0–14	PFS 7	II,III
FEC 90	Zielinski[38] (*n* = 135)	500/90/500 Q3W	84	3	OR 51 CR 5	OS 25 PFS 9	I
TH (T = pac)	Gasparini[46] (*n* = 62)	80/2–4 mg/kg Q1W	13	2	OR 75 pCR 22	PFS 10	III
A	O'Brien[47] (*n* = 255)	60 Q3W	7	3	OR 38	OS 22 PFS 8	I
CMF	Tannock.[48](*n* = 66)	600/40/600 Q3W	–	3	OR 30 CR 2	OS 16 PFS 7	II
Liposomal A	O'Brien[47] (*n* = 254)	50 Q4W	2	1	OR 33	OS 21 PFS 7	I
G/vino	Dinota[49] (*n* = 34)	1000^{d1+8}/25^{d1+8} Q3W	20	0	OR 53 CR 15	–	III
Dose-dense regimens							
DD epidox/C + G-CSF	Stöger[50] (*n* = 24)	100/600 Q2–3W + G-CSF	–	27	OR 61 pCR 26	–	II
DD epidox/C	Stöger[50] (*n* = 24)	100/600 Q2–3W	–	13	OR 56 pCR 11	–	II

a The list of regimens in this table is not exhaustive.
b Includes data for grade 4 neutropenia only.
c 20% of the patient population received treatment as second- or later-line chemotherapy for metastatic or advanced local disease.

Table 4 – Treatment regimens commonly used for the treatment of breast cancer in Europe and their associated risk of FN: second-line or later therapy for metastatic disease[a]

Chemotherapy regimen	References	Dose (mg/m^2 unless otherwise indicated)	Risk of grade 3–4 neutropenia (%)	Risk of FN (%)	Response rates (%)	Survival rates (%)	Level of evidence
FN risk >20%							
Vino/F	Bonneterre[51] (n = 90)	$25^{d1+5}/750^{d1-5}$ Q3W	14–67	22	OR 39 CR 4	OS 15 PFS 5	I
FN risk 10–20%							
T (T = doc)	Bonneterre[51] (n = 86); O'Shaughnessy[52] (n = 256); Vogel[53] (n = 465)	100 Q3W	82	13–17	OR 43 CR 7	OS 12–16 PFS 4–7	I
G/vino	Donadio[54] (n = 51); Gennatas[55] (n = 86)	$1000^{d1+8}/25^{d1+8}$ Q3W	11–48	0–2[b]	OR 33–36 CR 0–8	OS 14–18 PFS 5–11	III
TX (T = doc)	O'Shaughnessy[52] (n = 255); Levy[56] (n = 152)	$75/2500^{d1-14}$ Q3W	82	12–13	OR 32 CR 3	OS 15 PFS 6–8	I
A	Norris[57] (n = 149)	60 Q3W	86	10	OR 30 CR 3	OS 14 PFS 6	I
Vino	Jones[58] (n = 115)	30 Q1W	75	10	OR 16 CR 5	OS 8 PFS 3	I
G/carb	Nasr[59] (n = 30)	1000^{d1+8}/AUC4.5 Q3W	50	10	OR 30 CR 0	PFS 5	III
FN risk <10%							
TG (T = doc)	Levy[56] (n = 153)	$75/1000^{d1+8}$ Q3W	85	8	OR 32 CR 5	PFS 8	I
G/cis	Seo[60] (n = 33)	$1250^{d1+8}/75$ Q3W	–	7	OR 30 CR 0	OS 15 PFS 7	III
G/cis	Heinemann[61] (n = 38)	$750^{d1+8}/30^{d1+8}$Q3W	–	5	OR 40 CR 5	OS 14 PFS 6	III
Vino/X	Nole[62] (n = 49)	$12.5–25^{d1+3/8}/1000–2500^{d1-14}$ Q3W	74	2	OR 37 CR 2	PFS 7	III
TH (T = pac)	Seidman[63] (n = 95)	90/2–4 mg/kg Q1W	6	2	OR 61 CR 5	–	III
Weekly T (T = pac)	Perez[64] (n = 212)	$80^{d1,8+15}$ Q4W	15	1	OR 22 CR 2	OS 13 PFS 5	III
TH (T = doc)	Montemurro[65] (n = 42)	75 Q3W + 2–4 mg/kg Q1W	76	0	OR 67 CR 17	PFS 9	III
X	Reichardt[66] (n = 136); Fumoleau[67] (n = 126)	2500^{d1-14} Q3W	0	1–14	OR 15–28 CR 1–4	OS 10–15 PFS 4–5	III
Dose-dense regimens							
DD TG (T = pac) + G-CSF	Vici[68] (n = 39)	150/1500 Q2W + G-CSF	8	0	OR 53 CR 6	OS 20 PFS 9	III
DD T/F/LV (T = pac) + G-CSF	Nistico[69] (n = 51)	80/300/10 Q1W + G-CSF	0	0	OR 52 CR 6	OS 14 PFS 8	III

a The list of regimens in this table is not exhaustive.
b Data only available for FN that led to hospitalisation.

considered (Fig. 1).[4] Nevertheless, patients should still be evaluated for FN risk before each cycle (as in Fig. 2).

7.2. *Patient-related risk factors for FN*

Patients with MBC are at a high risk of FN because of their advanced disease and due to previous cytotoxic therapy and/or radiotherapy. Identical cytotoxic treatment regimens can therefore be associated with different FN risks when used at different disease stages. AC, for example, is associated with a higher FN incidence in the first-line MBC setting than in the adjuvant/neoadjuvant setting (Tables 1 and 3).[24,32,35] Furthermore, MBC patients being offered chemotherapy may have additional risk factors such as bone marrow involvement or age $\geqslant$ 65 years.[4] In future, scoring systems, such as that developed by Schwenkglenks and co-workers,[8] may be useful in assessing patients' overall FN risk. As with adjuvant/neoadjuvant treatment, the indiscriminate use of prophylactic antibiotics in MBC patients is discouraged.[4]

7.3. *Regimen-related risk factors for FN*

Despite the general aim to avoid toxicity, some regimens used in MBC are associated with high levels of myelosuppression

and FN (Tables 3 and 4). In the first-line cytotoxic treatment of MBC, regimens that have been associated with a FN risk of ⩾20% (thus warranting G-CSF primary prophylaxis) include anthracyclines plus a taxane. The choice of taxane may further influence FN risk, docetaxel plus doxorubicin having a higher FN risk than paclitaxel plus doxorubicin.[32,33,35] Doxorubicin plus paclitaxel has also been reported to have a much lower risk of FN (8%) in a study where the infusions of the two drugs were separated by 24 h.[39] To date, there are no published data on the use of G-CSF with these regimens in MBC. Table 3 also shows regimens with FN risk in the range of 10–20% when used as first line treatment for MBC. Again, patient factors should be assessed to determine whether G-CSF primary prophylaxis is required. Vinorelbine and paclitaxel monotherapies have been associated with FN risks of <10%.[43,45,46]

In later lines of therapy for MBC, between 10% and 20% of patients experience FN when treated with docetaxel with or without capecitabine, or vinorelbine monotherapy.[51–53,56,58] One phase III study investigated the efficacy of G-CSF in reducing the incidence of FN in this risk range and setting.[53] Here, G-CSF was shown to reduce the incidence of FN associated with docetaxel 100 mg/m^2 monotherapy from 17% to 1%. Lower dose docetaxel monotherapy (80 mg/m^2), docetaxel (75 mg/m^2) plus gemcitabine, capecitabine with or without vinorelbine and paclitaxel monotherapy all have FN risks below 10%.[56,62,64,66,67]

There is some evidence of a correlation between the number of myelosuppressive agents used to treat malignant disease and the risk of FN.[75] Therefore, it may be possible to reduce FN risk by prescribing monochemotherapy at or near the maximum tolerated dose, in preference to polychemotherapy, especially if the latter is known to be highly myelosuppressive. Certainly, there is a school of thought in the treatment of MBC that advocates, for most patients, a sequential monotherapy approach for which there is some supportive evidence.[83] However, inspection of Tables 3 and 4 shows that monotherapy regimens are not uniformly less haematotoxic than combination regimens. For example, in the post-first line setting, single-agent docetaxel in higher dose[51–53] of 100 mg/m^2 is associated with a greater FN rate (10%) than a number of polychemotherapy regimens (Table 4). All regimens must therefore be assessed for FN risk on an individual basis.

Trastuzumab combined with chemotherapy is now a standard of care in the treatment of HER2-positive MBC (Tables 3 and 4).[84] When added to paclitaxel monotherapy, trastuzumab did not increase the risk of FN from 2%, although the incidence of grade 3 and grade 4 neutropenia was slightly increased from 7% to 13%.[46] However, when trastuzumab was added to docetaxel monotherapy, FN increased from 17% to 23% – suggesting that primary prophylaxis with G-CSF should be considered.[85] This combination also saw an increase in the incidence of grade 3 and grade 4 neutropenia from 22% to 32%. These data, together with some recent data presented on the combination of paclitaxel and lapatinib, a small molecule tyrosine kinase inhibitor of HER2, suggest that the addition of an anti-HER2 targeted therapy to chemotherapy may increase the risk of neutropenia, and thus, perhaps FN.

Dose-dense regimens are also being used in the context of MBC treatment. In first-line treatment of advanced breast cancer, dose-dense epidoxorubicin plus cyclophosphamide without granulocyte–macrophage (GM)-CSF support has been compared to the same regimen with GM-CSF support delivered to two different schedules.[50] Prophylactic GM-CSF allowed a significant increase in the delivered dose-intensity of treatment which was achieved with negligible increase in the FN rate. However, there was no significant difference in overall response rate between the treatments, probably because of the small size of the three treatment groups ($n \leqslant 23$). In a further study, G-CSF prescribed with dose-dense paclitaxel/gemcitabine in the palliative setting was associated with an overall response rate of over 50% (including some complete remissions) and no reported incidences of FN.[68]

8. Implications of the EORTC guidelines for clinical practice

The prevention of FN and severe neutropenia is important not only to avoid FN-related morbidity, but also for maintaining chemotherapy dosing schedules. Hence, the new guidelines from EORTC, ASCO and NCCN on appropriate use of G-CSF to prevent neutropenic complications of chemotherapy are welcome. The principal impact of the guidelines is that many more patients qualify for primary prophylaxis with G-CSF due to the lower threshold for its use (overall FN risk ⩾20%), increased recognition of patient factors that contribute to FN, and the increasing use of dose-dense chemotherapy regimens.

Oncology centres are encouraged to implement these new guidelines. All patients should be individually assessed for FN risk prior to receiving chemotherapy, with G-CSF prophylaxis administered where appropriate. The development of validated FN risk scoring systems will help to achieve this goal, but there is already evidence that even simple FN risk assessment tools can have a dramatic impact. For example, the introduction of methodical FN assessment with prescription of G-CSF to those at ⩾20% risk reduced FN-related hospitalisation by 78% at one centre in the US.[86] Effective implementation of these guidelines therefore has potential to benefit both patients and the healthcare system, given the high costs associated with FN management (e.g. hospitalisation, and high-dose antibiotic use).

On the basis of retrospective data, some authors have suggested a possible small increase in the risk of secondary malignancies associated with G-CSF use.[87] The benefit:risk ratio remains in favour of G-CSF, however, through its facilitation of chemotherapy delivery and prevention of life-threatening FN.

The decision to prescribe G-CSF prophylaxis must, however, be accompanied by effective use of these agents. The EORTC guidelines state that G-CSF formulations (filgrastim, pegfilgrastim and lenograstim) are similarly efficacious and no individual agent is recommended over another (Fig. 1).[4] Pegfilgrastim is a pegylated formulation of G-CSF that is administered once per cycle.[88] Clinical trials have shown a single dose of pegfilgrastim to be as efficacious as daily filgrastim, 10–11 daily doses of which were required to ensure absolute neutrophil count recovery within the normal range.[89,90] In practice, however, daily G-CSF is frequently given for fewer than 10 days per cycle. In the Gepartrio trial ($n = 1256$), the efficacy of four regimens for primary prophylaxis of FN and related toxicities was assessed in successive

cohorts of patients receiving TAC neoadjuvant chemotherapy.[78] Pegfilgrastim with/without ciprofloxacin was significantly more effective than 'current practice' daily G-CSF (6 days of filgrastim or lenograstim from Day 5) or ciprofloxacin in preventing FN (5% and 7% versus 18% and 22% of patients; all $p < 0.001$), grade 3 and grade 4 neutropenia, and leukopenia.[78]

9. Conclusions

The value of prophylactic G-CSF in the management of chemotherapy-induced neutropenia has been reported in the recent EORTC guidelines.[4] In this article, we have reviewed EORTC recommendations in the context of adjuvant/neoadjuvant treatment of early stage breast cancer and treatment of MBC. Whatever the setting, FN risk should be individually assessed with respect to patient-related factors, chemotherapy regimen and treatment intent. If the patient is at an overall $\geqslant$20% risk of FN, G-CSF primary prophylaxis is recommended. For chemotherapy regimens with 10–20% risk of FN, particular attention should be paid to patient-related factors that may increase the overall risk. The use of CSFs in treating the existing infection is not recommended unless expert antibiotic management fails. Prophylactic use of antibiotics is not recommended, but may be necessary in specific patient groups.

These guidelines represent the application of evidence-based medicine and as such should be implemented in daily practice. Effective implementation will provide benefits for both patients and healthcare systems.

Conflict of interest statement

Christoph Zielinski has received speaker honoraria from Roche, Eli Lilly, Sanofi-Aventis and Merck Darmstadt and has served on Advisory Boards or attended meetings organised by Roche, Novartis, Eli Lilly, Amgen and Merck Darmstadt. David Cameron has received honoraria and research funding from Amgen, and honoraria from Chugai. Miguel Martin has served as consultant for Sanofi-Aventis, Pfizer, Roche and Novartis and has received speakers' honoraria from Bristol-Myers Squibb, Pharmamar, Novartis, Roche and Glaxo-SKF. Matti Aapro has received grants from and serves on an Advisory Board and Speaker's Bureau for Amgen, F. Hoffmann La-Roche and Sanofi-Aventis. Ahmad Awada and Tanja Cufer have no conflicts of interest.

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