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Position Paper

2010 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

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ABSTRACT

Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality and also a significant dose-limiting toxicity in cancer treatment. Patients developing severe (grade 3/4) or febrile neutropenia (FN) during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy. This may impact the success of treatment, particularly when treatment intent is either curative or to prolong survival.

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In Europe, prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs), such as filgrastim (including approved biosimilars), lenograstim or pegfilgrastim is available to reduce the risk of chemotherapy-induced neutropenia. However, the use of G-CSF prophylactic treatment varies widely in clinical practice, both in the timing of therapy and in the patients to whom it is offered. The need for generally applicable, European-focused guidelines led to the formation of a European Guidelines Working Party by the European Organisation for Research and Treatment of Cancer (EORTC) and the publication in 2006 of guidelines for the use of G-CSF in adult cancer patients at risk of chemotherapy-induced FN. A new systematic literature review has been undertaken to ensure that recommendations are current and provide guidance on clinical practice in Europe. We recommend that patient-related adverse risk factors, such as elderly age ($\geqslant$65 years) and neutrophil count be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. It is important that after a previous episode of FN, patients receive prophylactic administration of G-CSF in subsequent cycles. We provide an expanded list of common chemotherapy regimens considered to have a high ($\geqslant$20%) or intermediate (10–20%) risk of FN. Prophylactic G-CSF continues to be recommended in patients receiving a chemotherapy regimen with high risk of FN. When using a chemotherapy regimen associated with FN in 10–20% of patients, particular attention should be given to patient-related risk factors that may increase the overall risk of FN. In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF support is recommended. Similarly, if reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis may be used to maintain chemotherapy. Clinical evidence shows that filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents to prevent FN and FN-related complications where indicated. Filgrastim biosimilars are also approved for use in Europe. While other forms of G-CSF, including biosimilars, are administered by a course of daily injections, pegfilgrastim allows once-per-cycle administration. Choice of formulation remains a matter for individual clinical judgement. Evidence from multiple low level studies derived from audit data and clinical practice suggests that some patients receive suboptimal daily G-CSFs; the use of pegfilgrastim may avoid this problem.

1. Introduction

Chemotherapy-induced febrile neutropenia (FN) is a potentially fatal complication of cancer treatment, when it heralds infection and sepsis, and is seen most often during the initial cycles of myelosuppressive therapy.[1–8] Prevention of FN reduces hospital admissions, antibiotic usage and the need for dose reductions or delays in chemotherapy administration, which are associated with a poorer cancer outcome.[9–13]

Prophylactic administration of daily granulocyte-colony stimulating factor (G-CSF; filgrastim [Neupogen®] and lenograstim [Granocyte®]) or once per cycle administration of the pegylated form of G-CSF (pegfilgrastim, [Neulasta®])[14–18] provides protection for patients at risk of FN. In 2005, a European Guidelines Working Party was set up by the European Organisation for Research and Treatment of Cancer (EORTC) to systematically review available published data and derive evidence-based recommendations on the appropriate use of G-CSF in adult patients receiving chemotherapy; they first published their recommendations in 2006.[19] Since then, changes have occured in several areas, including our improved understanding of predisposing factors, the development of risk models and the availability of appropriate scoring systems. The risk of FN is increased by the recent trend for using dose-dense treatment schedules and the incorporation of taxanes and targeted agents into widely used chemotherapy regimens. With regard to the use of daily G-CSF versus once-per-cycle pegylated G-CSF, additional evidence has emerged since publication of the last EORTC guidelines. In addition, two further filgrastim biosimilar molecules (daily G-CSF) have been approved in Europe: XM02 and EP2006. These molecules are marketed by various companies using different trade names: Ratiograstim® (filgrastim; XM02), Filgrastim ratiopharm, Ratiopharm GmbH; Biograstim (filgrastim; XM02), CT Arzneimittel GmbH; Tevagrastim® (filgrastim; XM02), Teva Generics GmbH; filgrastim Zarzio® (EP2006), Sandoz GmbH; and filgrastim Hexal® (EP2006), Hexal Biotech Forschungs GmbH.[20–25]

These developments highlight the need to reassess current evidence and to update the existing guidelines regarding the prophylactic use of G-CSF.

A stringent and standardised definition of FN helps unify patient management algorithms. Febrile neutropenia is defined as an absolute neutrophil count (ANC) of $<0.5\times10^9$/L, or $<1.0\times10^9$/L predicted to fall below 0.5×10^9/L within 48 h, with fever or clinical signs of sepsis.[26] Currently, the European Society for Medical Oncology (ESMO) defines fever in this setting as a rise in axillary temperature to >38.5 °C sustained for

at least one hour.[26] It is suggested that therapy be initiated if a temperature of >38.0 °C is present for at least 1 hour or a reading of >38.5 °C is obtained on a single occasion.[27]

Some of the adverse consequences of chemotherapy-induced FN occur as a result of treatment delays and dose reductions. These have the potential to adversely affect tumour control.[28–37] For instance, poor outcome in cancer patients has been attributed to failure to deliver planned chemotherapy regimens for lymphoma,[38] breast cancer,[39] lung cancer[40] and ovarian cancer.[41] Prevention of chemotherapy-induced FN is, therefore, a clinical priority for patients undergoing treatment for solid tumours and lymphoma.

Progress has been made in our knowledge of what factors increase the risk of FN and in our ability to identify patients requiring G-CSF prophylaxis or antibiotic treatment or both. A variety of factors have now been implicated in the risk of developing FN, including tumour type (breast, lung, colorectal, lymphoma and ovarian), chemotherapy regimen and patient-related risk factors.[42–47] Patients who experience one episode of FN are at high risk of subsequent episodes, particularly after the occurrence of severe and prolonged neutropenia.[4,48]

Recognising patients at risk for complications of FN can be achieved using risk indices, such as those developed by the Multinational Association for Supportive Care in Cancer (MASCC) (Table 1).[49,50] Using the MASCC score, patients with a score of 21 or more points are considered at low-risk, while all other patients are considered at high risk of infectious complications. Identifying patients at risk of bacteraemia facilitates appropriate initiation of antibiotics.[51] Recent studies illustrate the impact of FN occurrence on hospitalisation and mortality, showing inpatient mortality rates of 9.5–12.5%.[52,53] In addition, a study of hospital practice in Pakistan has provided level IV evidence that G-CSF reduced in-hospital mortality (pneumonia or sepsis) from 20% to 4% and confirmed older age as a risk factor.[54]

The use of antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of neutropenia[55,56] is still contentious. Though widely practiced for managing patients with haematological malignancies usually without G-CSF, the same is not true for those being treated for other cancers. Two meta-analyses[57,58] and a systematic review[59] indicate that evidence is too limited to allow conclusions to be drawn regarding the relative merits of antibiotic versus CSF primary prophylaxis. A combined strategy may be appropriate in some settings. For example, in patients with breast cancer treated with docetaxel-based therapy, ciprofloxacin alone provides suboptimal prophylaxis against FN compared with pegfilgrastim plus ciprofloxacin.[60] Some authors recommend fluoroquinolone prophylaxis for patients receiving chemotherapy for haematological malignancies or high-dose chemotherapy for solid tumours in which prolonged (6 weeks) neutropenia is expected.[61] This cautious recommendation takes into account the finding that, in randomised controlled trials in patients receiving chemotherapy, routine fluoroquinolone prophylaxis has been shown to lead to an increase in resistance amongst Gram-positive and Gram-negative isolates compared with non-prophylaxed controls in randomised controlled trials in patients receiving chemotherapy.[56] The clinical consequences of this are unclear and it is important to avoid unwarranted use of antibiotics to lower the risk of drug resistance.[62]

Table 1 – MASCC risk index.

Characteristic	Score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma or no previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age < 60 years	2

MASCC, Multinational Association for Supportive Care in Cancer.

The intensity (frequency or total dose) of chemotherapy is a major factor to be taken into account when assessing the risk of FN and likely efficacy of G-CSF prophylaxis. Dose-dense (increased frequency), rather than dose-intense (increased dose) chemotherapy is increasingly used in an attempt to improve long-term clinical outcomes, often with the use of G-CSF support.[63] Several studies suggest that dose-dense chemotherapy or immunochemotherapy regimens have survival benefits when compared with standard regimens.[38,64–70]

However, any potential risk of secondary cancer arising from a shift away from standard chemotherapy should be considered. The Surveillance, Epidemiology, and End Results (SEER) analysis of patients with breast cancer aged ⩾65 years showed an incidence of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) of 1.77% amongst 906 patients receiving growth factor support compared with 1.04% amongst the 4604 patients not receiving CSF. There were, however, substantial differences between the two patient populations, e.g. in this study, patients receiving growth factor tended to have positive lymph nodes and received either more intense radiation therapy or high dose cyclophosphamide treatment.[71] These findings raised concern that G-CSF use in a high-dose setting amongst breast cancer patients could be associated with a high risk of secondary MDS or AML. However, an analysis of US registry data carried out to resolve this issue shows that the overall risk is small, even amongst elderly patients.[72] A meta-analysis of randomised, controlled trials indicates that a small increased risk of AML/MDS (approximately 4 per 1000 cases) is associated with the use of particular chemotherapy schedules in combination with G-CSF support.[73] In subgroup analyses, a significant increase in risk of AML/MDS was observed where G-CSF support was associated with a greater total dose of chemotherapy (Mantel–Haenszel relative risk [RR] = 2.334, $P = 0.009$) but not when the planned total dose of chemotherapy with G-CSF was the same in each study arm, such as dose-dense schedules. Furthermore, all-cause mortality was decreased in patients receiving chemotherapy with G-CSF support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.[73]

Current guidelines from the USA (American Society of Clinical Oncology [ASCO],[74] National Comprehensive Cancer

Network [NCCN]),[43] Canada[75] and Europe (EORTC[19] ESMO[76]), consistently advocate a risk threshold of 20% for routine G-CSF support in patients with solid tumours and lymphoma.[74] This threshold was established after the results from two large clinical trials demonstrated substantial reduction in FN incidence at this level of risk[5,66] and is supported by modelling studies.[44] Another recent trend is the addition of taxanes to commonly-used regimens for many solid tumours (docetaxel, doxorubicin, cyclophosphamide [TAC], fluorouracil/epirubicin/cyclophosphamide/docetaxel FEC-D); these are associated with an increased risk of FN and grade 4 neutropenia, with studies of patients in the UK showing FN rates >20%.[77–80] When treating chronic lymphocytic leukaemia (CLL), the improved efficacy made possible by frontline combination therapies (fludarabine/cyclophosphamide [FC] or FC-rituximab [FCR]) is accompanied by increased myelosuppression and high rates of grade 3–4 neutropenia, which may result in increased infection-related mortality (IRM).[81–84]

Evidence exploring these issues was gathered from the literature and is presented below, compiled with the evidence previously described.[19] These updated guidelines are intended to complement previously published ESMO guidelines on the use of colony-stimulating factors for prevention of chemotherapy-induced FN in patients with cancer.[26]

2. Methodology

Questions considered pertinent to G-CSF use across Europe were defined prospectively by the EORTC G-CSF Guidelines Working Party (Appendix 1). The computerised searches of MEDLINE, PreMEDLINE, EMBASE and The Cochrane Library used to support the 2006 guidelines (31st December 1994 to 16th September 2005) have been previously described.[19] These searches have now been extended to cover the period to 21st July 2009. Studies involving children <18 years of age or patients with leukaemia were excluded, as were cost analyses. Relevant articles 'in press' and additional papers identified by members of the working party were included in limited instances. Four appendixes are presented containing Supplementary information, together with a summary of the references used to draw up these guidelines according to study type (Appendix 3). Inclusion was not limited to a particular definition of FN and consequently the data cover a range of FN definitions. Reference lists of recent reviews and identified meta-analyses were scrutinised manually and any primary papers considered relevant were included. To avoid duplication and skewing of results, data from papers included in meta-analyses were used solely to answer questions not addressed by the meta-analysis, and full publications arising from congress presentations previously cited as abstracts were only included if they could answer questions not previously covered. In addition to the electronic database and meta-analyses, abstract books from key international congresses were searched manually to identify relevant evidence presented at meetings held between April 2006 and the end of December 2009. Where individual publications cited in the 2006 guidelines were superceded by meta-analysis data, the original publications were removed as evidence. The meetings reviewed and the search terms used were as previously reported.[19] Authors of relevant abstracts were contacted and any subsequent publications missed or 'in press' were included. Evidence was weighted using ASCO methodology (Table 2), according to study design, with the level of evidence lowered if the data were inferential. As before, all questions were considered for each study and positive and negative evidence recorded. All new data were reviewed and graded as shown in Table 3. This information was used in combination with the citations in the 2006 guidelines to identify any changes needed in each evidence-based recommendation.

Table 3 – Grade of recommendations applied by the EORTC G-CSF Guidelines Working Party.

Grade	Type of supporting evidence
A	Evidence of type I or consistent findings from multiple studies of types II, III or IV
B	Evidence of types II, III or IV and findings are generally consistent
C	Evidence of types II, III or IV but findings are inconsistent
D	Little or no systematic empirical evidence

EORTC, European Organisation for Research and Treatment of Cancer; G-CSF, granulocyte colony-stimulating factor.

3. Results and discussion

3.1. *Commentary on recommendation 1: patient-related risk factors for increased incidence of FN and complications of FN*

The previous EORTC guidelines were able to identify certain independent patient risk factors for FN, based on 11 stud-

Table 2 – Levels of evidence applied by the EORTC G-CSF Guidelines Working Party.

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or 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
IV	Studies such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

EORTC, European Organisation for Research and Treatment of Cancer; G-CSF, granulocyte colony-stimulating factor.

Table 4 – Recent evidence for patient-related risk factors for febrile neutropenia.

Reference	95	92	46	93	94	96	97	99
Cancer	Breast cancer	Ovarian	SCLC	NHL	NHL	Various		Haematological
Breast Cancer								
Study design	Phase III RCT data model	Phase III RCT	Phase III RCT	Prospective observational study	Prospective observational study	Prospective observational study	Prospective observational study	Prospective observational study
Patient risk factor								
Older age (⩾65 years)	II+[a]	III+	III+	III+	III+			III+
Advanced disease/metastasis							III+	
No antibiotic prophylaxis								
Prior episode of FN								
No G-CSF use			III+	III+		III+[c]	III+	III+
Female gender			III+					
Haemoglobin <12 g/dL/anaemia					III+		III+[b]	
Cardiovascular disease				III+				
Renal disease						III+		
Abnormal liver transaminases						III+		
Planned high chemotherapy dose intensity				III+		III+	III+	III+
Poor performance and/or nutritional status	II+							
⩾1 comorbidity						III–		
Body surface area <2.0 m^2							III+	
Lower weight								III+
Low pre-treatment or pre-cycle ANC	II+				II+			
Serum albumin <3.5 g/dL				III+				
Prior chemotherapy	III+			III+				
Prior infection				III+				

ANC, absolute neutrophil count; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NHL, non-Hodgkin's lymphoma; RCT, randomised controlled trial; SCLC, small-cell lung cancer.

[a] Age ⩾ 59 years.

[b] Interaction between haemoglobin level and planned chemotherapy intensity.

[c] $P = 0.14$, cycle 1; $P = 0.02$, all cycles.

ies.[1,4,85–91] The updated literature search identified an additional nine studies assessing multiple patient-related risk factors.[46,92–99] of which one presented level IV evidence.[98] The more recent level I, II and III evidence is shown in Table 4.

The compiled results from the 2006 and 2009 searches confirm that older age (particularly ⩾65 years) is the patient-related factor most consistently associated with an increase in FN risk, being identified by one level I, three level II, four level III and two level IV studies. However, advanced age does not appear to increase risk further, as shown in a level III study of patients aged ⩾70 years in which further stratification by age alone (70–74 years, 75–79 years and ⩾80 years) did not increase the risk of haematological toxicity.[96]

Other adverse risk factors which were supported by level I or II evidence for increased risk of FN included: advanced stage of disease;[88] experience of previous episode(s) of FN;[1,46] lack of G-CSF use[1,93,97,99] and lack of antibiotic prophylaxis.[88] Because a previous episode of FN predisposes to further occurrence, it is important that the risk of FN and related complications are assessed at each cycle, and where appropriate, secondary prophylaxis with G-CSF is initiated. Level III evidence shows that the use of G-CSF as primary or secondary prophylaxis not only reduces risk of FN but also decreases the duration of those grade 4 neutropenia events which can occur despite prophylaxis.[46]

Levels III and IV evidence support prior chemotherapy and planned chemotherapy intensity as risk factors.[4,44,93,97–99] Data from the INC-EU prospective Observational European Neutropenia Study in non-Hodgkin's lymphoma (NHL) patients highlighted a history of prior chemotherapy (odds ratio [OR] 6.39; 95% confidence interval [CI] 1.72, 23.68; $P = 0.006$) and history of prior infection (OR 6.39; 95% CI 1.72, 23.68; $P = 0.006$) as adverse risk factors for FN.[93] Similarly, logistic regression data from the Impact of Neutropenia in Chemotherapy European study group (INC-EU) prospective Observational European Neutropenia Study in patients with breast cancer identified presence of vascular comorbidity (OR 2.29; 95% confidence interval [CI] 1.25, 4.20; $P = 0.007$), higher baseline bilirubin (OR 4.38; 95% confidence interval [CI] 1.25, 15.33; $P = 0.021$) and, as expected, baseline leucocyte count $<5 \times 10^9$/L (OR 0.87; 95% confidence interval [CI] 0.76, 0.99; $P = 0.037$) as adverse risk factors for FN.[99] Three recent studies (Table 4) have confirmed that chemotherapy intensity is the most important determinant of the risk of neutropenia.[97–99]

Several investigators have developed models for predicting neutropenia based on the current risk factors. Although as yet not validated on an independent database, these may prove invaluable clinical tools. For patients with haematological cancers, the following risk factors were selected for inclusion: chemotherapy myelosuppressive potential, underlying disease, baseline monocyte count <150 μL, low body surface area, use of prophylactic antimicrobial agents, use of prophylactic CSF, bone marrow involvement, stem-cell transplantation and the interaction between the first cycle of a treatment line and the baseline haemoglobinaemia.[97] The maximum computed score is 35 (the higher the score, the higher the probability of FN). Using a cut-off of 15 for the first cycles and 10 for the other cycles, this model has high negative predictive value (89.1%) but a lower positive predictive value (42.7%), meaning that it is of greatest benefit when used to determine which patients are not at risk of FN. For patients with breast cancer, a panel of pre-treatment haematological indices have been used to predict the risk of neutropenia. Stratifying patients into 5 groups based on baseline ANC and absolute lymphocyte count (ALC) showed a 2.8-fold variation in risk of any neutropenic event and 5.3-fold variation in FN between the separate groups.[98] Modelling of risk factor in patients with breast cancer using older age, lower weight, higher planned dose intensity or number of planned cycles, vascular comorbidity, lower baseline white blood cell count and higher baseline bilirubin correctly identified 320 of 434 patients at risk.[99] Other prospective registries have also been established to record data on different clinical measures (haematological function, neutropenic events, dosing schedule, comorbidities, performance status, etc.) during each cycle of chemotherapy in patients with several common tumour types in order to develop more accurate multivariate risk models.[7,100,101] Validation of such risk factor modelling is ongoing. While one prospective study has implicated the presence of cancer related inflammation and baseline lymphopaenia as risk factors for docetaxel-induced neutropenia (level III evidence) in patients with advanced cancer, further data are needed.[102] The current findings and recommendations on evaluation of risk factors remain in line with our previously published guidelines[19] and with current United States (UK) and United Kingdom (UK) guidelines.[43,74,103,104]

3.2. *Recommendation 1: patient-related risk factors for increased incidence of FN*

Patient-related risk factors should be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include: advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and absence of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotic prophylaxis for patients undergoing treatment for solid tumours or lymphoma is not recommended either by this working party or the EORTC Infectious Disease Group. *Recommendation grade: B.*

3.3. *Commentary on recommendation 2: chemotherapy regimens associated with increased risk of FN*

The risk of FN associated with individual chemotherapy regimens must be taken into account when evaluating the need for prophylactic intervention. A recent trend is the addition of targeted agents to established chemotherapy regimens. These new regimens have been shown to improve survival – for example, the addition of cetuximab or bevacizumab to chemotherapy in non-small cell lung cancer (NSCLC) patients.[105–107] While targeted agents are generally associated with a good toxicity profile, myelosuppression may be exacerbated. A large scale randomised study has demonstrated that the addition of cetuximab/vinorelbine/cisplatin significantly increased the incidence of grade 3/4 febrile neutropenia from 15% to 22% ($P = 0.0086$) and grade 3/4 sepsis from <1% cases to

Table 5 – Common chemotherapy regimens associated with intermediate or high risk of febrile neutropenia.

Malignancy	FN risk category (%)	Chemotherapy regimen and reference	FN risk (%)
Breast cancer	>20	AC → docetaxel[43,109,110]	5–25
		Docetaxel → AC[109]	40
		Doxorubicin/docetaxel[111,112]	33–48
		Doxorubicin/paclitaxel[43,86,113]	21–32
		TAC[43,60,114]	22–25 (no PP)
			5–7 (PEG-F PP)
		DD/DDG FEC[115]	71/59
		DDG[c] doxorubicin → paclitaxel → cyclophosphamide[116]	2 (with PP)
		DDG[c] doxorubicin/cyclophosphamide → paclitaxel[116]	2 (with PP)
		DDG epirubicin/cyclophosphamide[117]	8 (with PP)
	10–20	AC[b,43]	10–20
		Doxorubicin/vinorelbine[118]	15
		Docetaxel,[43,119]	16–17
		Capecitabine/docetaxel[43,119]	13
		Cyclophosphamide/mitoxantrone[120]	11
		FEC-D[77,80]	25–46 in clinical practice
		FEC-100[121,d]	13 despite PP
			17 despite SP
		AC[122,d]	14
		Epidoxorubicin/cyclophosphamide[a,123]	13
		CEF[117]	14
	<10	FEC 120[117,124]	9–14
		CMF[125,126]	0–3
		CMF oral[124]	1
		Doxorubicin/cyclophosphamide[120]	0–3
		Doxorubicin → paclitaxel → cyclophosphamide[116]	3
		Doxorubicin/cyclophosphamide → paclitaxel[116]	5
		FAC 50[127]	5
		Epirubicin/cyclophosphamide ± lonidamide[128]	7
Small cell lung cancer	>20	ACE[1,14,45,88,129,130]	24–57
		Topotecan[a,43,131]	28
		ICE[132]	24
		VICE[133]	70
		DDG[c] ACE[88,129]	34–56
		DDG[c] ICE[132]	18
		DDG[c] CAV → PE[134]	4
	10–20	CAV[135]	14
		Etoposide/carboplatin[43]	10–20
		Topotecan/cisplatin[43,136]	19
		Tirapazamine/cisplatin/etoposide/irradiation[137]	14
		CODE[138]	19
	<10	CAV → PE[138,139]	3–9
		Paclitaxel/carboplatin[140]	9
Non-small cell lung cancer	>20	Docetaxel/carboplatin[43,85]	26
		Etoposide/cisplatin[a,141]	54
		Cisplatin/vinorelbine/cetuximab[105]	22
	10–20	VIG[43,142]	25
		Paclitaxel/cisplatin[43,143]	16
		Docetaxel/cisplatin[143,144]	5–11
		Vinorelbine/cisplatin[145,146]	1–10
	<10	Paclitaxel/carboplatin[143,147,148]	0–9
		Gemcitabine/cisplatin[149,150]	1–7
		Gemcitabine/cisplatin[143]	4
		Bevacizumab/paclitaxel/carboplatin[106]	5.2

Table 5 – (*continued*)

Malignancy	FN risk category (%)	Chemotherapy regimen and reference	FN risk (%)
Non-Hodgkin's lymphoma/chronic lymphocytic leukaemia	>20	DHAP[43,151]	48
		ESHAP[43,151–153]	30–64
		R-ESHAP as salvage after prior rituximab (R)[154]	33.5%
		CHOP-21[4,155]	17–50
		DD/DDG[c] VAPEC-B[43,156]	44/23
		DD/DDG[c] ACVBP[18,43]	78/52
		Hyper CVAD + rituximab (Burkitt's lymphoma)[43]	
		ICE/R-ICE[43,157,158]	11.5–24 with PP
		Stanford V[159]	Grade 3–4 neutropenia, 25%
		MOPPEB-VCAD[159]	Grade 3–4 neutropenia, 49%
		FC[160]	35
		FC[82]	10%, despite PP[e]
		FCR[84]	Grade 3–4 neutropenia 33.7%
	10–20	ACOD[43,161]	11
		R-CHOP-21[43,161]	19
		Fludarabine/mitoxantrone[43,162]	11
		Dose adjusted EPOCH[163,164]	19% of cycles[163] 51[164]
		Mega CHOP-R-Ara-C cyclophosphamide (mantle cell)[165]	15
		RGemP[166]	61% grade 3 or 4 neutropenia
		RGemOx (elderly patients)[167]	43% grade 3 or 4 neutropenia[167]
Hodgkin's disease	>20	BEACOPP[168–170]	>90% grade 4 leukopenia[168]54% grade 3-4 neutropenia[169] 10% septic deaths[170]
		ABVD (Hodgkin's lymphoma)[171]	4
		CEC[169]	48% grade 3–4 neutropenia
		IGEV[172]	28% grade 3–4 neutropenia
Ovarian cancer	>20	Docetaxel[43,173]	33
		Paclitaxel[a,43,174]	22
	10–20	Topotecan[43,175,176]	10–18
	<10	Paclitaxel/carboplatin[177,178]	3–8
		Gemcitabine/cisplatin[179]	9
Urothelial cancer	>20	Paclitaxel/carboplatin[180]	25
		MVAC[181]	26
		DDGc MVAC[181]	10
Germ cell tumours	>20	BOP → VIP-B46	46
		VeIP[43,182]	67
	10–20	Cisplatin/etoposide[43,183]	10
		BEP → EP[87]	13
Colorectal cancer	10–20	5-FU/leucovorin[184,185]	1–15
		FOLFIRI[186,187]	3–14
	<10	FOLFOX[188,189]	0–8
		IFL[43,190]	3–7
		Irinotecan[191,192]	
Metastatic gastric cancer	>20	LVFU	20
		LVFU-cisplatin	40
		LVFU-irinotecan[d,193]	24
		DCF[194]	29
	>20	TC[195]	21
		TCF[195]	41
		ECF[195]	18
	10–20	Docetaxel-irinotecan[196,d]	14.9
		FOLFOX-6[197,d]	11

(*continued on next page*)

Table 5 – (*continued*)

Malignancy	FN risk category (%)	Chemotherapy regimen and reference	FN risk (%)
Other malignancies		Irinotecan (Metastatic colorectal cancer)[191,192]	2–7
	>20	TIC (head and neck cancers)[43,198]	30
		MAID (sarcoma)[43,199]	58
		Paclitaxel/cisplatin (cervical cancer)[43,200]	28
	10–20	Gemcitabine/irinotecan (pancreatic cancer)[43,147]	17
		Stanford V (Hodgkin's lymphoma)[159,171]	14
	<10	Doxorubicin/cisplatin (endometrial cancer)[201]	2
		TAP (endometrial cancer)[201]	3
		TPF (laryngeal cancer)[202]	10.9
Oesophagal	10–20	ECF	13.2
		ECX	10.5
		EOF	11.5
		EOX[203]	9.8

The abbreviations used are those in common usage in each indication: 5-FU, 5-fluorouracil; ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; AC, doxorubicin/cyclophosphamide; AC → T, doxorubicin/cyclophosphamide followed by docetaxel; ACE, doxorubicin/cyclophosphamide/etoposide; ACOD, doxorubicin/cyclophosphamide/vincristine/prednisolone; ACVBP, doxorubicin or mitoxantrone with cyclophosphamide/vindesine/bleomycin; Ara-C, cytarabine; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone; BEP → EP, bleomycin/etoposide/cisplatin followed by etoposide/cisplatin; BOP → VIP-B, bleomycin/vincristine/cisplatin followed by cisplatin/ifosfamide/etoposide/bleomycin; CAV, cyclophosphamide/doxorubicin/vincristine; CE, cyclophosphamide/epirubicin; CEC, cyclophosphamide/lomustine/vindesine/melphalan/prednisone/epidoxirubicin/vincristine/procarbazine/vinblastine/bleomycin; CEF, cyclophosphamide/epirubicin/5-FU; CHOP-21, cyclophosphamide/doxorubicin/vincristine/prednisone; CMF, cyclophosphamide/methotrexate/fluorouracil; CODE, cisplatin/vincristine/doxorubicin/etoposide; CVAD, cyclophosphamide, vincristine, adriamycin and dexamethasone; DCF, docetaxel/cisplatin/fluorouracil; DD, dose-dense; DDG, dose-dense with G-CSF; DHAP, cisplatin/cytarabine/dexamethasone; ECF, Epirubicin/cisplatin/fluorouracil; ECX, Epirubicin/cisplatin/capecitabine; EOF, Epirubicin/oxaliplatin/fluorouracil; EOX, Epirubicin/oxaliplatin/capecitabine; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; ESHAP, etoposide/methylprednisolone/cytarabine/cisplatin; FAC, fluorouracil/doxorubicin/cyclophosphamide; FC, fludarabine/cyclophosphamide; FCR, fludarabine/cyclophosphamide/rituximab; FEC, cyclophosphamide/epirubicin/fluorouracil; FEC-D, FEC/docetaxel; FMD, fludarabine/mitoxantrone; FN, febrile neutropenia; FOLFIRI, 5-FU/l-folinic acid/d,l-folinic acid/irinotecan; FOLFOX, 5-FU/folinic acid/oxaliplatin; FN, febrile neutropenia; hyper CVAD, fractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone; ICE, ifosfamide/carboplatin/etoposide; IFL, irinotecan/5-FU/calcium folinate; IGEV, ifosfamide/Mesna gemcitabine, vinorelbine, G-CSF; LVFU, leucovorin-primed fluorouracil; MAID, mesna/doxorubicin/ifosfamide/dacarbazine; MOPPEB, mechlorethamine/vincristine/procarbazin/prednisone/etoposide/bleomycin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; PE, cisplatin/etoposide; PEG-F, peg-filgrastim; PP, primary prophylaxis; Q2 W, once every 2 weeks; R-CHOP-21, rituximab/CHOP; R-ESHAP, rituximab/etoposide/methylprednisolone/cytarabine/cisplatin; RGemP, rituximab/gemcitabine/methylprednisilone; RGemOx, rituximab/gemcitabine/oxaliplatin; R/ICE, ifosfamide/carboplatin/etoposide/rituximab; SP, secondary prophylaxis; Stanford V, mustard/doxorubicin/vinblastine/vincristine/bleomycin/etoposide/prednisolone; T → AC, docetaxel followed by doxorubicin/cyclophosphamide; TAC, docetaxel/doxorubicin/cyclophosphamide; TAP, paclitaxel/doxorubicin/cisplatin; TC, docetaxel/cyclophosphamide; TCF, docetaxel/cyclophosphamide/fluorouracil; TIC, paclitaxel/ifosfamide/carboplatin; TPF, docetaxol/cisplatin/5-fluorouracil; VAPEC-B, vincristine/doxorubicin/prednisolone/etoposide/cyclophosphamide/bleomycin; VelP, vinblastine/ifosfamide/cisplatin; VICE, vincristine/ifosfamide/carboplatin/etoposide; VIG, vinorelbine/ifosfamide/gemcitabine.
Dosing details of those regimens not covered in the EORTC 2006 Guidelines[19] are presented in Appendix 4.

[a] In these studies patients had adverse risk factors and may have been at increased risk of FN.

[b] Although this risk level is indicated by the NCCN analysis, some clinicians believe AC to be a low-risk regimen.

[c] DDG indicates dose-dense regimens supported by primary prophylactic G-CSF to reduce the incidence of neutropenia. Please note that data shown in this table are examples only.

[d] Phase II clinical trial data.

[e] Ninety four percent of patients received filgrastim.

2% ($P = 0.053$). Similarly, increased incidence of febrile neutropenia has been reported in patients receiving bevacizumab and chemotherapy compared with chemotherapy alone.[106,108] In CLL patients, neutropenia is more common amongst subjects receiving rituximab than those receiving chemotherapy alone.[84] Table 5 shows an updated summary of FN risk with commonly used chemotherapy regimens. Thresholds for these categories were >20%, 10–20% and <10%. Full details of regimen dosing are available in Appendix 4.

Level IV evidence from audits of clinical practice indicates that the regimen FEC-100 followed by docetaxel has a high rate of FN (25–46%) in the absence of primary prophylaxis.[77,80] Three-quarters of FN episodes occurred during docetaxel treatment.

All identified trials generally focused on overall results of therapy rather than FN incidence and the definitions of FN are heterogeneous. In addition, diverse FN rates are reported for the same chemotherapy regimens, possibly as a consequence of differences in the study populations and delivered dose intensity. In some studies, antibiotic prophylaxis was specified as being part of the protocol. However, in the majority of studies, it is unclear if this was the case and, therefore, no specific analysis was possible. Despite this heterogeneity it is evident that certain regimens in common usage are associated with the development of FN and FN-related complications.

Table 6 – Intensive chemotherapy regimens supported by G-CSF.

Malignancy	Chemotherapy regimen	Level of evidence	Reference
Dose-dense regimens (increased frequency)[a]			
Breast cancer	FEC[b]	I	204
	Epirubicin/cyclophosphamide[b]		117
	Doxorubicin → paclitaxel → cyclophosphamide[b]		116
	Doxorubicin/cyclophosphamide → paclitaxel[b]		116
	Epirubicin/paclitaxel or epirubicin → paclitaxel → CMF		68
	Epirubicin/cyclophosphamide	III	122
	Docetaxel → epirubicin → DEC	II	211
	MMM[b]	III	20
NHL	R-CHOP/CHOP[b]	II	66
		II	212
		II	213
			70
		III	209
			210
	DA-EPOCH	III	163,164
	RICE/ICE	III	157,158
HD	IGEV		172
	BEACOPP	III	250
SCLC	ACE[b]	II	136
			67
	CAV → PE (alternating weekly)[b]		134
	VICE (⩾Q2 W, not fixed)[b]		133
	CODE (QW)		138,[b]
	Cisplatin/epirubicin/paclitaxel		205
	Docetaxel/cisplatin	III	207
NSCLC	Cisplatin/vindesine/mitomycin C (PVM)[b]	II	139
Urothelial cancer	MVAC[b]	II	181
Dose-intense regimens (increased dose)			
HD	BEACOPP[b]	II	168
NHL	11 drugs over 8 cycles[b]	IV	251
Ovarian cancer	Paclitaxel[b]	II	174
SCLC	ACE[b]	II	136
	Carboplatin/etoposide/lenograstim		206
	Paclitaxel/teniposide or etoposide/cisplatin	III	208
Dose-modified regimens (withdrawal of one drug and increase in the dose of the remainder)			
Breast cancer	Epirubicin/cyclophosphamide with withdrawal of 5-FU	I	117,[b]
	Cyclophosphamide with high-dose mitoxantrone and withdrawal of doxorubicin	III	120

5-FU, 5-fluorouracil; ABVD, doxorubicin/bleomycin/vinblastine/decarbazine; ACE, doxorubicin/cyclophosphamide/etoposide; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone; CAV → PE, cyclophosphamide/doxorubicin/vincristine followed by cisplatin/etoposide; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CMF, cyclophosphamide/methotrexate/fluorouracil; CODE, cisplatin/vincristine/doxorubicin/etoposide; DA-EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin/rituximab; DEC, docetaxel/epirubicin/cyclophosphamide; ICE, ifosfamide/carboplatin/etoposide; IGEV, ifosfamide/Mesna/gemcitabine/vinorelbine/G-CSF; FEC, cyclophosphamide/epirubicin/fluorouracil; HD, Hodgkin's disease; MMM, mitoxantrone/methotrexate/mitomycin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; Q2W, once every two weeks; PVM, cisplatin/vindesine/mitomycin C; Q2W, once every 2 weeks; QW, once per week; R-CHOP, rituximab/CHOP; RICE, rituximab/ICE; SCLC, small-cell lung cancer; VICE, vincristine/ICE.

[a] The dose-dense regimens were given every 2 weeks, unless otherwise specified.

[b] References cited in Aapro.[19]

3.4. *Recommendation 2: chemotherapy regimens associated with increased risk of FN*

"Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens, summarised in Table 5. *Recommendation grade: A/B* (depending on the evidence for each chemotherapy regimen). It should be noted that this list is not comprehensive and there may be other drugs or regimens associated with an increased risk of FN."

3.5. *Commentary on recommendation 3: G-CSF to support intensive chemotherapy regimens*

Dose-dense (increased frequency) or dose-intense (increased dose) chemotherapy is increasingly used in an attempt to improve long-term clinical outcomes. The previous search identified 15 full manuscripts,[19] of which 14 clearly support the use of prophylactic G-CSF to facilitate the delivery of dose-dense or -intense chemotherapy (Table 6).[66,67,116,117,120,133,134,136,138,139,168,174,181,204,205] Thirteen additional publications were identified in the updated searches (Table 6).[63,68,70,122,172,206–213] Multiple studies have confirmed that, because the time to neutrophil recovery is around 12 d, pegfilgrastim can be conveniently administered together with chemotherapy in patients receiving treatment at 14 d intervals.[63,70,209–211,214]

Most of the clinical trials shown in Table 6 present data in which haematological toxicity was similar in the dose-dense or -intense arms compared with standard therapy. However, in some cases G-CSF support can enable dose intensification concurrent with reduction of neutropenic events. In patients with small-cell lung cancer (SCLC), for example, comparison of conventional carboplatin plus etoposide (CE) with dose-intensified CE combined with G-CSF support showed that grade 3/4 neutropenia occurred in 69.4% of patients in the conventional arm versus 37.5% in the dose-intensified group ($P = 0.009$).[206] Similarly, in the UK National Cancer Research Institute Lymphoma Group study comparing R-CHOP-14 (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; 14 d intervals) plus G-CSF with R-CHOP-21 (21 d intervals) in diffuse large B-cell lymphoma (DLBCL) patients age $\geqslant$ 18, grade 3/4 neutropenia occured in 31% versus 57% patients and infection in 17% versus 22% patients.[212] In addition, a study by the Groupe d'Etude des Lymphomes de l'Adulte in elderly patients in which G-CSF support was at physician discretion compared eight cycles of therapy based on R-CHOP-14 (an arm in which 90% of patients received G-CSF support) with that based on R-CHOP-21 (an arm in which 68% of patients received G-CSF support).[213] Interim analysis demonstrated a higher grade 3/4 neutropenia incidence in the dose-dense than in the control arm, 83% versus 69%, indicating that dose-dense therapy requires G-CSF support.[213]

Evidence from trials published before and after 2006 identifies four studies providing level II evidence of G-CSF use to support dose-dense or -intense chemotherapy.[129,138,215,216] The incidence of FN was higher in the dose-dense or -intense arms compared with the standard-dose chemotherapy arms.[129,138,215,216] As the use of prophylactic G-CSF support does not completely abolish the increased risk of FN associated with intensification of chemotherapy, it remains important to use myeloid growth in settings when treatment has survival benefits. Maintaining dose intensity is likely to be particularly relevant where treatment is intended to be curative or to prolong survival.[217]

The previous searches revealed strong and consistent evidence for the use of G-CSF prophylaxis in order to maintain chemotherapy at the desired dose intensity and density and to minimise delays (10 of 11 publications identified).[1,2,18,87,134,139,180–182,218–221] Conversely, in one level III study of ovarian cancer, the provision of daily filgrastim prophylaxis beginning on day 3 of a myelotoxic high-dose paclitaxel regimen did not produce a significant reduction in the incidence of FN compared with the standard unsupported regimen.[174] A further study provided level II evidence that the addition of varying intensity schedules of open-label G-CSF to high-dose epirubicin/cyclophosphamide chemotherapy in patients with stages I and II breast cancer had no significant impact on the delivered dose-intensity compared with the non-G-CSF arms. This represents a setting in which G-CSF support would not have been recommended according to the present guidelines.[128]

Benefits of growth factor administration in terms of intended dose frequency and intensity have been confirmed by a level I meta-analysis of nine randomised controlled trials (seven with G-CSF),[222] of which all except one showed better dose intensity in the growth factor arm than the control arm.

An additional five publications (meta-analysis = 1, level II = 1, level III = 1, level IV = 2), identified in the updated literature search also support the prophylactic use of G-CSF to maintain chemotherapy dose intensity/density in conjunction with standard chemotherapy regimens.[37,38,210,223–225]

Results from the Impact of Neutropenia in Chemotherapy European study group (INC-EU) prospective observational study in breast cancer and patients with lymphoma (level III evidence) show that primary prophylaxis with G-CSF had a strongly protective effect against reduced relative dose intensity (RDI) administration in patients with lymphoma (OR 0.46; 95% CI 0.23, 0.93; $P = 0.029$) but was not significant in patients with breast cancer.[37]

In the level I evidence meta-analysis by Kuderer et al., 10 trials were identified which used RDI as an outcome.[223] The average RDI amongst control patients ranged from 71.0% to 95.0% with a mean of 86.7%. Amongst G-CSF-treated patients the average RDI ranged from 91.0% to 99.0%, with a mean of 95.1%. None of the 10 G-CSF treatment arms reported a mean RDI of <90%, whereas 6 of 10 control groups reported a mean RDI of <90%, with four control arms averaging an RDI of $\leqslant$85%. This represents an 8.4% increase in dose intensity. Average RDI was significantly higher in patients who received G-CSF compared with control patients ($P < .001$).

Clamp et al. reported long term follow-up data from a randomised trial using G-CSF to maintain dose intensity of vincristine/doxorubicin/ prednisolone/etoposide/cyclophosphamide/bleomycin (VAPEC-B) in patients with NHL.[224] The authors found that 10-year freedom from progression was better in the patients receiving G-CSF. Deaths from progressive disease numbered 10 in the G-CSF arm and 19 in the placebo arm ($P = 0.02$).

While G-CSF support allows the use of intensive chemotherapy regimens that may improve survival, current evidence remains mixed regarding an improvement in progression-free survival (PFS) or overall survival (OS) in this setting.[206,215,222–224] As yet, data comparing R-CHOP-14 plus G-CSF support with R-CHOP-21 cannot allow conclusions regarding survival to be drawn.[212,213]

Compiled data from 2005 and 2009 searches reveal that two level I studies[219,222] and six level II studies[124,128,130,212,215,226] fail to provide any evidence that haematopoietic growth factors significantly improve OS, disease-free survival (DFS) or PFS, compared with chemotherapy alone. The level I meta-analysis

by Bohlius et al., in patients with lymphoma, indicates that, compared with no prophylaxis, both G-CSF (nine studies, 2192 patients) and granulocyte–macrophage colony-stimulating factor (GM-CSF; one study, 29 patients) did not improve overall survival (hazard ratio [HR] 0.97; 95% CI 0.87, 1.09).[222] As described in the study by Clamp et al., G-CSF support reduced rates of death from lymphoma progression. However, at a median follow up of 15.7 years, no significant differences were seen in OS and PFS, although it should be noted that 11 deaths in the G-CSF arm and 5 in the control arm were unrelated to treatment.[224]

In contrast, one level II study found a significant survival advantage when dose-intense ACE (doxorubicin/cyclophosphamide/etoposide) was given with G-CSF support, compared with standard ACE alone.[67] In this study survival rates with and without G-CSF were 47% and 39%, respectively ($P = 0.04$; 95% CI 0.65, 0.99).

A level I meta-analysis in lymphoma and solid tumour patients (13 randomised controlled trials, 3122 patients) reported that the addition of G-CSF to standard chemotherapy resulted in a reduction in early mortality from 5.7% to 3.4%, with a weighted summary RR of 0.60 (95% CI, 0.43–0.83; $P = 0.002$). Reductions in early mortality with G-CSF were observed amongst studies of filgrastim (RR = 0.60; 95% CI, 0.41–0.89; $P = 0.010$) and pegfilgrastim (RR = 0.36; 95% CI, 0.13–0.99; $P = 0.047$) but not lenograstim (RR = 0.84; 95% CI, 0.38–1.83; $P = 0.657$).[223] However, this subgroup comparison must be interpreted cautiously and considered as a generating hypothesis only. A small level II study ($n = 65$) has suggested a tendency for improved long-term survival in patients with favourable-prognosis SCLC receiving VICE chemotherapy (vincristine/ifosfamide/carboplatin/etoposide) plus G-CSF compared with chemotherapy alone (2-year survival rate: 32% [95% CI 16%, 48%] versus 15% [95% CI 2%, 27%], respectively), although the difference was not tested statistically.[133]

In the treatment of lymphoma particular patient subgroups may show survival benefits when G-CSF support is added to standard chemotherapy[70] or used to support intensive chemotherapy.[155] In younger, previously untreated patients with intermediate-risk aggressive NHL, assigned to receive either eight courses of standard CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) ($n = 239$) without G-CSF support or six courses of intensified (I)-CHOP with G-CSF support ($n = 238$), there was no statistically significant advantage in terms of OS. However, when patients were stratified into low-intermediate- and high-intermediate-risk according to the International Prognostic Index (IPI), patients in the first group had improved 6-year OS (67% versus 52%; $P = 0.05$), DFS (58% versus 45%; $P = 0.06$), and event free survival (EFS) (41% versus 30%; $P = 0.21$) when treated with I-CHOP compared with standard CHOP.[70] Preliminary data from a prospective observational study of 4458 consecutive adult patients receiving cancer chemotherapy indicated that patients receiving primary prophylaxis with pegfilgrastim experienced better PFS (HR = 0.65; 95% CI 0.46, 0.92; $P = 0.0109$) and OS (HR = 0.41; 95% CI 0.21, 0.81; $P = 0.0079$) than those without such support.[217]

One level II study included a subset analysis that showed a marginal benefit in 5-year overall survival for patients treated with CHOP plus G-CSF (45 of 101 patients died), compared with CHOP alone (62 of 104 patients died; $P = 0.045$).[155]

The relationship of RDI with OS has been underlined in two recent retrospective analyses using G-CSF to support R-CHOP-21 in patients newly diagnosed with DLBCL.[227,228] Both reports indicate that RDI was a significant factor associated with OS.[227,228]

Similar findings have been obtained from Belgian and UK audit data. The treatment of DLBCL with chemotherapy was retrospectively evaluated in 273 patients who had received at least three cycles of CHOP – like regimens in Belgium between 1995 and 2000. In total, 15% of patients received <80% average relative dose intensity (ARDI).[38] In 210 patients treated with CHOP-21 (77% of the CHOP-like group), median survival was 7.08 years in those who received >90% of the ARDI, significantly longer than in those who received ⩽90% of the ARDI ($P = 0.002$). Dose reductions and/or delays were mainly due to haematological toxicities. Data from the UK Audit of Lymphoma patients, which identified 78 cases who received treatment with CHOP-21, confirmed this finding both alone and in combination with the Belgian dataset ($n = 289$).[37] In the UK dataset reduced survival was associated with RDI ⩽ 90% (HR 1.42, 95% CI 0.88–2.28; $P = 0.014$). In the combined dataset, RDI ⩽ 90% was associated with reduced survival with a HR of 1.77, CI 1.12–2.79, $P = 0.014$).[37]

3.6. *Recommendation 3: G-CSF to support chemotherapy*

In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment. *Recommendation grade: A.*

If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival. *Recommendation grade A.* Where treatment intent is palliative, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. *Recommendation grade: B.*

3.7. *Commentary on recommendation 4: impact of the overall FN risk on G-CSF use*

Results from compiling the searches carried out in 2005 and 2009 show substantial evidence that the prophylactic use of G-CSF reduces the incidence of chemotherapy-associated FN in a wide range of malignancies. The strongest evidence supporting the use of G-CSF to prevent FN comes from three level I meta-analyses.[218,222,223] In the lymphoma meta-analysis, of four studies analysed, the underlying risk of FN (neutrophils below 1.0×10^9/L) was at least 36% and RR reduction with G-CSF was approximately 26% (RR 0.74; 95% CI 0.62, 0.89).[222] In a review of solid tumours, the underlying FN risk was approximately 50% and RR reduction with G-CSF was approximately 50%.[218] Similarly, in a meta-analysis of patients with lymphoma or solid tumours across 15 randomised controlled trials (nine trials with filgrastim, five with lenograstim and one with pegfilgrastim) in which the overall underlying risk of FN was 37%, the RR reduction with G-CSF was 46% (RR 0.54; 95% CI 0.43, 0.67; $P = <0.001$).[223]

It should be noted that while the meta-analyses supported the use of G-CSF to reduce FN, some individual studies did not. Additional evidence in favour of G-CSF prophylaxis was found in two level II studies not included in any of the meta-analyses.[128,229]

As described previously,[19] there is evidence that patients scheduled to receive myelosupressive chemotherapy regimens experience the most significant benefit from G-CSF prophylaxis. Three level I studies[1,218,222] and one level IV study[2] demonstrated a significant reduction in the incidence of FN when patients received a chemotherapy regimen associated with FN in ⩾20% patients. A further study that compared a weight-adapted dose of pegfilgrastim to G-CSF in patients at the 20–40% risk level showed a similar result.[16] Kuderer et al. found a greater FN reduction in populations at lower risk of FN.[223] While the majority of studies in this analysis have an underlying FN risk of >40%, this analysis included a single pegfilgrastim study treating 928 patients with breast cancer, in which the underlying FN risk was approximately 17% and RR reduction with G-CSF was approximately 90%.[5] Exclusion of this trial from analysis eliminated the inverse correlation of underlying FN risk and risk reduction by growth factor support in the remaining 2535 patients.[223]

Level III evidence from the INC-EU prospective European neutropenia study supports the use of G-CSF to reduce the incidence of FN in lymphoma and patients with breast cancer[37] and confirms that patients scheduled to receive certain chemotherapy regimens obtain the most benefit from G-CSF prophylaxis. In multivariate analysis, clinically relevant factors that were significantly associated with cycle 1 FN included increasing planned cyclophosphamide dose and increasing planned etoposide dose.[37,93] An analysis for cycle 1 FN in 240 patients with lymphoma showed that prophylactic G-CSF was strongly protective (OR 0.18; 95% CI 0.03, 0.94; $P = 0.042$).[93] Similarly, prophylactic use of G-CSF protected against grade 4 neutropenia in patients with breast cancer.[99]

Level III evidence from a further prospective observational study in elderly patients (age ⩾ 70 years) with lymphoma or solid tumours has also confirmed benefits of G-CSF.[96] In this study, primary CSF prophylaxis significantly decreased neutropaenic complications, defined as the occurrence of severe or FN in cycles 1–4, by 64% (OR 0.36; 95% CI 0.21, 0.62; $P = 0.0002$).[96] This study also confirmed that anthracycline or platinum-based regimens were associated with an increased risk of FN.

Level IV evidence from audit data of patients with breast cancer treated with FEC-D in clinical practice demonstrated a reduction in rates of FN from 46% to 8.6% with the use of primary daily G-CSF prophylaxis, usually given from days 5 to 10. The authors comment that this course may not be optimal and further improvements may be possible with early or prolonged treatment.[77]

Level I evidence to support the use of primary prophylaxis with G-CSF in patients with breast cancer receiving chemotherapy associated with ⩾15% risk of FN has been reported in an integrated analysis of 11 randomised clinical trials (eight randomised clinical trials, two prospective observational trials, and one retrospective trial).[230] A three-step approach was taken for the comparative analysis. Firstly, the homogeneity of patient populations was assessed within the pegfilgrastim primary prophylaxis (PPP) and conventional practice (CP) groups. In the second step, homogeneity between these treatment groups was assessed. Finally, a generalised linear mixed model was fitted to the primary outcome measure using SAS software (Proc Glimmix procedure). The type of neutropenia prophylaxis (PPP or CP) was included in the modelling process as a fixed effect and the study was included as a random effect. Results showed that compared with CP, pegfilgrastim support was associated with an overall reduction in FN from 16% to 5% and a reduction in first-cycle FN from 10% to 3% ($P < 0.0001$). The OR rate (95% CI) for reduction in FN was 0.124 (0.08, 0.194). When the analysis was adjusted for covariates that could influence in the risk of FN, age and disease stage, the overall reduction was from 29% to 5% and the first-cycle FN reduction was from 21% to 3%.[230] The risk of FN-related hospitalisation was significantly lower in the G-CSF PPP group compared with the CP group (OR 0.20).

There is also preliminary level III evidence that G-CSF may help prevent or treat mucositis and stomatitis.[60,181,231]

In summary, recommendations 1–3 above identified a number of factors that should influence the clinician when considering primary prophylactic G-CSF for patients scheduled to receive chemotherapy. Each of these factors should be incorporated into an assessment of the overall risk of FN for each patient on an individual, case-by-case basis. Therefore, while there is not a strictly defined threshold above which G-CSF should be used, recent studies confirm that G-CSF has clinical benefits for patients at ⩾20% risk of FN. While the current guidelines have been produced in an effort to standardise and improve the quality of care for chemotherapy patients, it remains important for the reader to note that these are not designed to supercede nationally focused guidelines which are available in many cases.[232] It should be noted that the current review did not include evidence derived from economic models, as these must be applied on a country-by-country basis.

3.8. *Recommendation 4: impact of the overall FN risk on G-CSF use*

The risk of complications related to FN should be assessed individually for each patient *at the beginning of each cycle*. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3) and treatment intent (recommendation 3). Prophylactic G-CSF is recommended when there is a ⩾20% overall risk of FN. When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. *Recommendation grade:* A.

3.9. *Commentary on recommendation 5: G-CSF in patients with existing FN*

Few studies have addressed the use of growth factors in patients with existing FN. One level I study presented evidence that when G-CSF or GM-CSF is used therapeutically in conjunction with standard therapy (intravenous antibiotics and

other supportive care) for patients with ongoing FN, there is a marginal but statistically significant improvement in FN-related events compared with standard treatment alone.[233] However, the authors of this meta-analysis point out that this result requires further investigation as the analysis was not adequately powered to observe the impact of CSF use on this outcome.

In addition, a level II randomised trial in 210 patients with solid tumours and high-risk FN showed that addition of G-CSF to broad-spectrum antibiotic treatment reduced the duration of neutropenia and hospitalisation.[234] In this study, patients randomly assigned to receive G-CSF had a significantly shorter duration of grade IV neutropenia (median, 2 d versus 3 d; $P = 0.0004$), antibiotic therapy (median, 5 d versus 6 d; $P = 0.013$) and hospital stay (median, 5 d versus 7 d; $P = 0.015$) than those in the control arm. In addition, the incidence of serious medical complications not present at the initial clinical evaluation was 10% in the G-CSF group and 17% in the control group ($P = 0.12$), including five deaths in each study arm.[234]

In the absence of studies restricted to patients with existing FN, infection-related mortality rates can be assessed as an outcome. The evidence to support the use of G-CSF to reduce the incidence of infection-related mortality is mixed. When used prophylactically, there is level I evidence that G-CSF either does[223] or does not[218,222] show a significant beneficial effect on infection-related mortality. In patients with lymphoma, meta-analysis of infection-related mortality with G-CSF versus control showed a relative risk (RR) of 0.93 (95% CI 0.51–1.74), indicating no significant reduction in infection-related mortality.[222]

In contrast, a recent level I evidence meta-analysis of 12 trials using standard therapy in adult patients with lymphoma and solid tumours showed a significant benefit in adding G-CSF. This study indicated that infection-related mortality was reduced from 2.8% to 1.5% by G-CSF support (RR 0.55; 95% CI 0.34, 0.90; $P = 0.018$).[223] The clinical relevance of the absolute risk reductions seen with G-CSF support in these studies remains to be determined.

Most clinical studies show that infection-related mortality rate in the control groups was low, resulting in a lack of power to detect a treatment effect.

As mortality is generally very low in clinical trials of patients with early disease, more informative data might be obtained if the impact of G-CSF prophylaxis or treatment on infection-related mortality rates were to be examined in a 'real-life' setting. These findings and our recommendations are similar to those of ASCO,[74] and we continue to recommend that "*G-CSF should not be used routinely as adjunct therapy for the treatment of uncomplicated fever and neutropenia, but may be considered in patients who are at a higher risk of infection-related complications and have prognostic factors that are predictive of poor clinical outcome.*"

3.10. Recommendation 5: G-CSF in patients with existing FN

"Treatment with G-CSF for patients with solid tumours and malignant lymphoma and ongoing FN is indicated only in special situations. These are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infectious complications (such as severe sepsis or septic shock)." *Recommendation grade: B.*

3.11. Commentary on recommendation 6: choice of formulation

The 2006 EORTC guidelines for the use of different growth factors were based on 10 comparative studies that addressed the use of different haematopoietic growth factors for the prevention or treatment of chemotherapy-induced FN.[15,16,89,123,218,222,233,235,236]

There is evidence from four studies (one level I,[233] two level II[89,123] and one level III[222]) indicating that daily G-CSF (filgrastim, lenograstim or unspecified G-CSF) and GM-CSF (molgramostim, sargramostim or unspecified GM-CSF) are comparable in efficacy. There is level I evidence that the two non-pegylated G-CSFs, filgrastim and lenograstim have similar efficacy against FN and FN-related end-points.[218] While this study identified a trend for a greater treatment effect with filgrastim in terms of reducing the risk of FN, documented infections and infection-related mortality, none were statistically significant.

When this manuscript was prepared, two biosimilars to daily filgrastim had been approved in Europe and clinical evidence for two of these was identified by literature search (see note about a third biosimilar, nivestim, added after discussion). Clinical evidence from a meta-analysis[237] based on three phase III trials[238–240] and two supportive studies[241,242] indicates that XM02 is similar to filgrastim. Several phase I and one phase III studies including pharmacodynamic/pharmacokinetic parameters provide the evidence that filgrastim EP2006 is similar to filgrastim.[243] Given that biosimilar products are not generic products, a switch from filgrastim to a biosimilar is considered a change in clinical management.[244] Due to multiple variations in the complex production process, biological products tend to differ from each other and from the previously approved agent. Consequently, to ensure traceability and thus robust pharmacovigilance, clinicians are encouraged to identify a product by brand name and ensure that no changes in treatment are made without informing both physician and patient

Compiled results from 2005 and 2009 searches identified five studies comparing prophylactic administration of the pegylated G-CSF, pegfilgrastim, with filgrastim.[15–17,235,236] There are key differences between this compound and alternative myeloid growth factors, as pegfilgrastim exerts a prolonged effect in the presence of continued neutropenia. Unlike daily G-CSF, pegfilgrastim is not eliminated rapidly and rates of turnover are regulated by neutrophil level, with the result that pegfilgrastin persists for approximately 14 d or until neutrophil recovery is achieved.[210,214] In one dose-finding study and two small phase II trials (evidence level III), powered to demonstrate equivalence, filgrastim and pegfilgrastim were shown to have similar efficacy against FN-related end-points.[16,235,236] Data from two phase III, multicentre, double-blind, randomised trials showed a lower incidence of FN in patients given pegfilgrastim compared with filgrastim[15,17] although in one study this difference was not

Table 7 – Incidence of febrile neutropenia from comparative phase III and II pegfilgrastim studies.

Study	Arm	Cancer	*n*	Dosing	Incidence of FN (all cycles),[a], *n* (%)	*p*
Phase III[17]	Filgrastim	Breast	149	Daily sc injection of 5 μg/kg filgrastim starting on day 2 for up to 14 days or until ANC reached 10×10^9/L post nadir	27 (18)	0.029
	Pegfilgrastim	Breast	147	Single sc injection of pegfilgrastim 100 μg/kg on day 2 of each cycle	14 (9)	
Phase II[16]	Filgrastim	Breast	25	Daily sc injection of 5 μg/kg filgrastim starting on day 2 for up to 14 d or until ANC reached 10×10^9/L post nadir	2 (12)	NS
	Pegfilgrastim	Breast	46	Single sc injection of pegfilgrastim 100 μg/kg on day 2 of each cycle	5 (11)	
Phase III[15]	Filgrastim	Breast	75	Daily sc injection of 5 μg/kg filgrastim starting on day 2 for up to 14 d or until ANC reached 10×10^9/L post nadir	15 (20)	NR
	Pegfilgrastim	Breast	77	Single sc injection of pegfilgrastim 6 mg on day 2 of each cycle	10 (13)	
Phase II[235]	Filgrastim	Lymphoma	33	Daily sc injection of 5 μg/kg filgrastim starting on day 2 for up to 14 d or until ANC reached 10×10^9/L post nadir	19	NR
	Pegfilgrastim		33	A single sc injection of pegfilgrastim 100 μg/kg on day 2 of each cycle	21	
Phase II[236]	Filgrastim	NHL	13	Daily sc injection of 5 μg/kg filgrastim starting on day 2 for up to 14 d or until ANC reached 10×10^9/L post nadir	1 (8)	NS
	Pegfilgrastim		13	Sc injection of pegfilgrastim 100 μg/kg on day 2 of each cycle	0 (0)	

ANC, absolute neutrophil count; FN, febrile neutropenia; NHL, non-Hodgkin's lymphoma; NR, not recorded; NS, not significant; sc, subcutaneous.

[a] FN recorded in cycles 1 and 2 for Vose et al.[235] FN rates reported in ⩾1 cycles for Grigg et al.[236]

statistically significant. In these studies, the efficacy and safety of a single pegfilgrastim dose were compared with daily filgrastim in 157[15] and 310[17] patients with stage II–IV breast cancer receiving up to four cycles of doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks. The FN incidence in patients who received pegfilgrastim versus filgrastim was 13% versus 20% and 9% versus 18%, respectively.

Detailed results from these five trials are shown in Table 7. The original trials were not powered to detect superiority of one agent over another in terms of a decrease in the rates of febrile neutropenia. The data from these trials have, therefore, been further assessed in a meta-analysis focussing on reduction in incidence of febrile neutropenia.[245] The meta-analysis indicated superiority of pegfilgrastim over filgrastim for this end-point, with a pooled RR of 0.64 (95% CI 0.43–0.97),[245] although as indicated by the data presented in Table 7 showing the characteristics of the included trials, the results are considered to be level II/III evidence and do not allow a definitive conclusion.

Without G-CSF support, the AT regimen (docetaxel/doxorubicin) has been reported in a dose finding study to be associated with an FN rate of 38%.[246] A recently reported non-randomised study[60] has allowed comparisons between different prophylactic regimens to be made. In this study, 2432 patients with breast cancer were treated with TAC (given on day 1, 3-weekly for 6 cycles). Prophylaxis of FN was consecutively intensified throughout the study by three protocol amendments. Patients received either primary prophylaxis with daily G-CSF on days 5–10 ($n = 377$; 2400 cycles), pegfilgrastim 6 mg on day 2 ($n = 305$; 1930 cycles) or pegfilgrastim plus ciprofloxacin ($n = 321$; 1890 cycles).[60] Pegfilgrastim with or without ciprofloxacin was significantly more effective than daily G-CSF or ciprofloxacin in preventing FN (5% and 7% versus 18% and 22% of patients; all $P < 0.001$). However, the timing and duration of daily G-CSF treatment, while consistent with common clinical practice, did not comply with current guidelines. ESMO recommendations state administration of daily G-CSF should start 24–72 h after chemotherapy and continue until ANC recovery,[26] which typically takes 10–11 d. Suboptimal use of daily G-CSF may, therefore, have compromised patient outcome in this study.

For a full assessment of the relative merits of myeloid growth factors in clinical practice, relative clinical effectiveness may be as relevant as relative clinical efficacy. The ability to deliver G-CSF as recommended can have an impact on clinical effectiveness. While other forms of G-CSF, including biosimilars, are administered by a course of daily injections, pegfilgrastim allows convenient once-per-cycle administration. Two recent publications were identified which present level IV evidence showing that in clinical

practice, administration of daily G-CSF injection does not conform to clinical guidelines[247,248] and which highlight the need to maintain adequate G-CSF dosing to reduce the risk of FN.[230,247,248] The LEARN study from Spain has assessed patterns of use of daily G-CSF (111 patients) and pegfilgrastim (70 patients) in clinical practice and showed that pegfilgrastim was associated with numerically fewer neutropenia-related complications. In this retrospective observational study, the median number of daily G-CSF injections given as primary prophylaxis was 6 (range 1–11) and as secondary prophylaxis was 5 (range 1–11).[247] This means that many patients were not treated optimally, according to current guidelines.

Similarly, a retrospective observational study of 4362 US cancer patients who experienced FN after receiving standard cancer therapy with G-CSF support showed that daily G-CSF was initiated on average 7.7 d (standard deviation [SD] 3.0) after treatment at first cycle and 4.9 d for subsequent cycles, while pegfilgrastim was initiated on average at 2.4 d (SD 3.2).[248] The OR of developing FN amongst patients who received filgrastim versus pegfilgrastim was 1.41 (95% CI 1.02, 1.96; $P = 0.04$) after adjusting for patient and chemotherapy regimen characteristics. It should be noted that filgrastim was administered in 2001 and pegfilgrastim in 2003.

As discussed, suboptimal use of daily G-CSF may have compromised patient outcome in the GEPARTRIO study and the data (level III evidence) from this investigation indicate that pegfilgrastim may provide benefits over filgrastim if current guidelines for daily administration cannot be realised.[60]

In addition, data on the use of G-CSF to support R-CHOP-21 in NHL patients[249] show that while 52% of patients were considered to have an FN risk of $\geqslant$20%, only 23% of these received treatment (either daily G-CSF or pegfilgrastim). Febrile neutropenia led to a substantial number of hospitalisations.

Overall, while it is important to be aware that additional effectiveness in clinical practice may be made possible by the use of pegfilgrastim, strong evidence, derived from multiple, large-scale studies, is currently lacking to confirm superior clinical efficacy in head-to-head trials. The advantages of pegfilgrastim in terms of convenience and a prolonged clearance profile are supported by results obtained from several low level studies derived from audit data and clinical practice.

3.12. *Recommendation 6: choice of formulation*

Filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated. Filgrastim biosimilars are now also a treatment option in Europe. *Recommendation grade:* A.

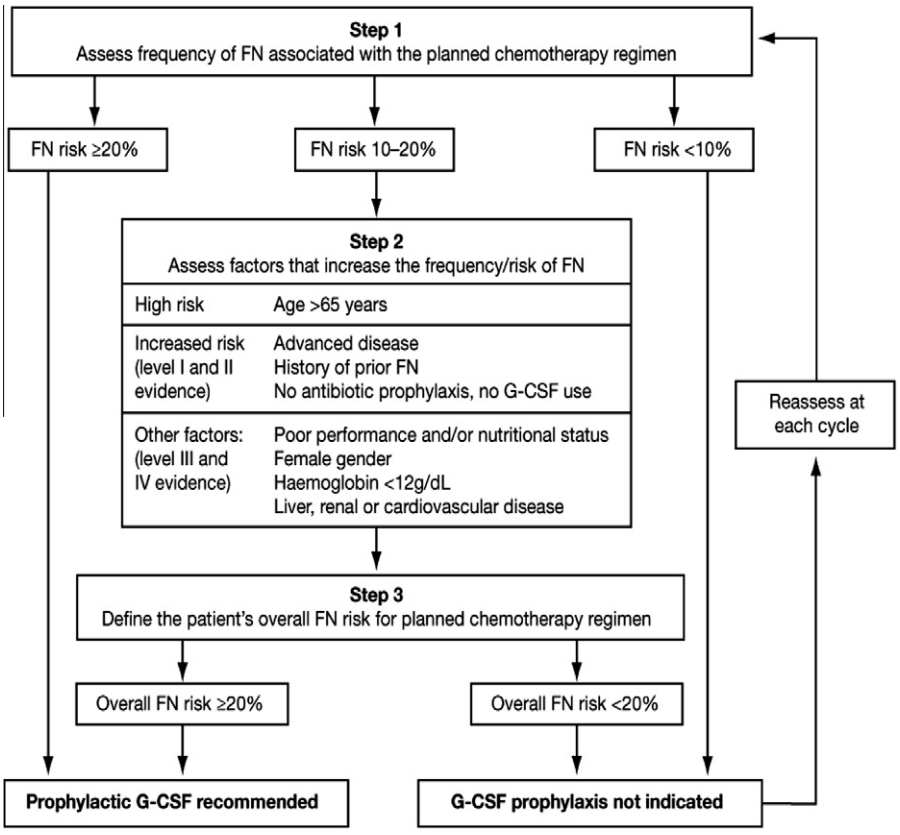

Fig. 1 – Patient assessment algorithm to decide primary prophylactic G-CSF usage. FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor. Primary prophylaxis: start G-CSF in first cycle 24-72 hours after end of the first chemotherapy and continue through all cycles (when appropriate as per cycle reassessment). Secondary prophylaxis: start G-CSF if a neutropenic event was observed in the previous cycle.

4. Conclusion

In conclusion, we have produced up-to-date recommendations for G-CSF use that are relevant to current European clinical practice, as summarised in Fig. 1.

These may help to optimise local protocols and patient management strategies in hospitals across Europe and, in turn, improve patient care and clinical outcomes. This review has allowed alignment of the 2010 EORTC guidelines with evidence available until end of 2009, including review of the 2009 NCCN and 2006 ASCO guidelines. The guidelines also place a strong emphasis on the assessment of overall FN risk, which should be individually examined for each patient before each cycle of chemotherapy.

The data review and recommendations detailed above represent a statement of consensus of the EORTC G-CSF Guidelines Working Party based on their interpretation of evidence identified using the methodology described. Any clinician using or referring to these guidelines is expected to use good clinical judgement and experience to determine appropriate care and treatment for each patient.

Disclaimer

The EORTC offers no guarantees of any kind nor can it be held liable for any consequences which might derive from using these guidelines. Constant developments in the field mean that some recent information might be missing. Thus a third biosimilar, nivestim was recently approved by the European Medicines Agency (EMA).[252]

Conflict of interest statement

Julia Bohlius, Lissandra Dal Lago, Nora Kearney, Ruth Pettengell, Vivianne C. Tjan-Heijnen, Jan Walewski, and Damien Weber have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.10.013.

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