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Position Paper

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

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ABSTRACT

Chemotherapy-induced neutropenia is not only a major risk factor for infection-related morbidity and mortality, but is 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 on

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the success of treatment, particularly when treatment intent is either curative or to prolong survival. The incidence of severe or FN can be reduced by prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs), such as filgrastim, lenograstim or pegfilgrastim. 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. While several academic groups have produced evidence-based clinical practice guidelines in an effort to standardise and optimise the management of FN, there remains a need for generally applicable, European-focused guidelines. To this end, we undertook a systematic literature review and formulated recommendations for the use of G-CSF in adult cancer patients at risk of chemotherapy-induced FN. We recommend that patient-related adverse risk factors such as elderly age (⩾65 years), be evaluated in the overall assessment of FN risk prior to administering each cycle of chemotherapy. In addition, when using a chemotherapy regimen associated with FN in >20% patients, prophylactic G-CSF is recommended. When using a chemotherapy regimen associated with FN in 10–20% 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. Finally, studies have shown 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.

1. Introduction

Chemotherapy-induced febrile neutropenia (FN), is a serious side effect of cancer treatment, commonly occurring during the initial cycles of cytotoxic therapy[1–6] and increasing in frequency with both the depth and duration of neutropenia.[7,8] As well as having an impact on quality of life,[9] chemotherapy-induced FN predisposes patients with cancer to serious and often life-threatening infections.[10,11] Given the seriousness of FN, the majority of patients who develop this complication are admitted to hospital for evaluation and administration of broad-spectrum parenteral antibiotics.[11]

In addition to infections, chemotherapy-induced FN often also results in lengthy treatment delays and dose reductions, which have been shown to compromise treatment.[12–18] The risk of developing FN appears to depend on a variety of factors, including tumour type, chemotherapy regimen and patient-related risk factors.[10,19–21]

Clearly, prevention of chemotherapy-induced FN should be considered a clinical priority. However, there is considerable diversity in the strategies used to reduce the incidence of this complication. Recombinant human granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs) are the only agents currently available that can treat or prevent neutropenia and therefore reduce its associated complications.[10,19,22]

The use of antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of neutropenia,[23,24] remains a matter of debate despite the publication of a large meta-analysis[25] and a systematic review.[26] In these analyses, the provision of prophylactic antibiotics was significantly associated with a reduction in the incidence of FN and of infection-related mortality. The working party and the EORTC Infectious Disease Group strongly suggest that caution be used; general antibiotic prophylaxis could lead to the emergence of resistance, so it is essential that a balance is achieved between potential harms and benefits to patients.[27]

In Europe, prophylactic administration of G-CSF (filgrastim and lenograstim) or the more recently introduced pegylated form of G-CSF (pegfilgrastim), which has a longer duration of action,[28–31] is generally used to treat at-risk patients. However, the criteria for determining patients who are at risk of developing FN or prolonged neutropenia has not been clearly defined. Patients who have experienced a neutropenic complication in a previous cycle of chemotherapy, may receive G-CSF to avoid another neutropenic event. Alternatively, chemotherapy may be delayed or doses reduced in subsequent cycles of treatment without administration of G-CSF. Chemotherapy delays or reductions resulting from an episode of FN may have detrimental clinical consequences, as they lead to a decrease in the chemotherapy dose delivered during a certain time period.[32] In addition, G-CSF is sometimes used therapeutically in order to reduce the severity and duration of ongoing neutropenia.[33,34]

Increasingly, G-CSF is being used prophylactically to support dose-dense and dose-intense chemotherapy regimens. Several examples suggest that dose-dense chemotherapy is associated with survival benefits over standard regimens.[35–39] In fact, the dose-dense and -intense regimen R-CHOP-14 is considered by many to be the new standard in non-Hodgkin's lymphoma (NHL) treatment. The superior survival benefits of this regimen compared to CHOP-14 have been suggested by two recent phase III trials.[40,41]

Given the wide diversity in G-CSF use, it is perhaps unsurprising that recommendations from current clinical

practice guidelines also vary significantly with regard to when and to whom G-CSF should be given. Previous guidelines from the American Society of Clinical Oncology (ASCO), advocated a risk threshold of 40% for routine G-CSF support in patients with solid tumours and non-myeloid malignancies.[10] Recent guidelines published by the National Comprehensive Cancer Network (NCCN), based solely on clinical data, advocate a 20% risk threshold.[19] These guidelines were based on a consensus approach and also recommend that both treatment intent and patient risk factors should be considered when determining the overall risk of a neutropenic event.

The guidelines developed by ASCO and NCCN are useful and comprehensive reference tools, but do not always reflect clinical practice in Europe, particularly as the chemotherapy regimens used in Europe are often different to those used in the USA. Therefore, there is a need to develop European guidelines for the use of G-CSF, in order to improve patient care and outcomes across Europe by use of consistent, evidence-based, patient management strategies. To achieve this, a G-CSF Guidelines Working party has been 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 for cancer. These guidelines are designed to complement previously published EORTC guidelines on the use of colony-stimulating factors in elderly patients with cancer.[42]

2. Methodology

Questions considered pertinent to G-CSF use across Europe were defined prospectively by the EORTC G-CSF Guidelines Working party (Appendix 1). Computerised literature searches of MEDLINE, PreMEDLINE, EMBASE and The Cochrane Library were undertaken to identify reports of relevant clinical studies (search terms are described in Appendix 2). To be considered relevant, the studies were required to be published in the English language between 31 December 1994 and 16 September 2005. Studies involving children $\leqslant$18 years of age or patients with leukaemia were excluded, as were cost analyses, as these lack international applicability. Relevant articles 'in press' and additional papers identified by members of the working party, were included in limited instances. During the review it became clear that additional information was needed in order to formulate recommendation 2 and a secondary search was therefore undertaken. Details of this search can be found in Appendix 3 and general information about the papers used in the completed literature review can be found in Appendix 4.

Study inclusion was not limited to a particular definition of FN, and consequently the data include a range of FN definitions. However, where stated, these definitions did not widely differ from the consensus statement of the Infectious Diseases Society of America (IDSA) fever and neutropenia guidelines panel.[11] In this report, fever is defined as a single oral temperature of $\geqslant$38.3 °C or a temperature of $\geqslant$38.0 °C for $\geqslant$1 h. Neutropenia is defined as a neutrophil count of <500 cells/mm^3 or <1000 cells/mm^3, predicted to fall below 500 cells/mm^3.

To ensure that all relevant articles were included, reference lists of the identified meta-analyses were interrogated manually and any primary papers considered relevant were included. However, data from these papers were used solely to answer questions not addressed by the meta-analysis, to avoid duplication and skewing of results.

In addition to the electronic database and meta-analysis review, abstract books from key international congresses were searched manually to identify relevant evidence presented at meetings held between 2003 and the end of December 2005. The meetings considered and search terms used are shown in Appendix 2. Authors of relevant abstracts were contacted and any subsequent publications missed or 'in press' were included.

The EORTC G-CSF Guidelines Working party used methodology published by ASCO in order to systematically review the data.[43] Owing to the large number of studies identified (>5000), it was agreed that the evidence review would be hierarchical. The search results were therefore investigated to identify meta-analyses, phase III studies, phase II studies, etc. Data from published meta-analyses were reviewed first to determine whether any of the questions could be answered. Where two or more meta-analyses had been published including some of the same papers to answer the same question, only the most recent analysis was considered. If any of the questions could not be answered using meta-analysis data then phase III studies were reviewed. This provided sufficient evidence to formulate all recommendations, with the exception of recommendation 2 (see above). Cost analyses were not considered (unless they specified relevant clinical data not included in the primary clinical paper) because it was agreed that they quickly become outdated and differences between national European healthcare systems limit their general applicability. All questions were considered for each study and positive and negative evidence recorded. For each question, evidence levels, as used by ASCO (Table 1), were applied according to study design. It was agreed that if a study was not powered to answer a particular question, but it offered data in support of the answer, the level of evidence for that question would be lowered. The body of evidence available to answer each question was reviewed,

Table 1 – 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	Evidence obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

Table 2 – Grade of recommendations applied by the EORTC G-CSF Guidelines Working party

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

graded (see Table 2) and used to formulate an evidence-based recommendation.

3. Results and discussion

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

Eleven studies examined the influence of patient-related factors on the risk of FN.[4,6,21,44–50] Looking at these publications, it was evident that certain independent patient risk factors exist for FN.

This review showed that older age (particularly ⩾65 years), was the patient-related factor most consistently associated with an increase in FN risk, being identified by one level I, two level II, one level III and two level IV studies (Table 3). Other adverse risk factors for patients included: advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and lack of antibiotic prophylaxis. These four factors were associated with levels I or II evidence for increased risk of FN. All other risk factors listed in Table 3 are associated with levels III or IV evidence only.

In addition to the studies shown in Table 3, two level II studies identified risk factors for the duration of hospitalisation in patients with established FN.[48,49] In these studies solid tumour diagnosis, >11 days since chemotherapy and fever of unknown origin were significantly associated with a reduction in the length of hospitalisation for FN. However, the following factors were not significant predictors of the duration of hospitalisation for FN: no GM-CSF use; low-risk chemotherapy; performance status; positive or negative blood cultures; longer interval from the first day of chemotherapy to randomisation; amount of antibiotic therapy.

EORTC elderly guidelines now recommend that prophylactic G-CSF is used to support the administration of planned doses of chemotherapy on schedule in standard chemotherapy settings in all elderly patients receiving myelotoxic chemotherapy.[42] Our recommendations and findings are also in agreement with those recently produced by the NCCN.[19]

It was notable that the majority of evidence was low level (level III–IV), which reflects the study designs and methodological limitations of the clinical prediction models used. Clearly, accurate and validated risk models that predict and quantify the risk of FN prospectively in individual patients would be invaluable.[21] In this regard, prospective registries have recently 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.[3,52,53] Validation of this risk factor modelling is ongoing and the results of this joint initiative are awaited with interest.

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 prior to 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 included: advanced stage of disease; experience of previous episode(s) of FN; lack of G-CSF use and lack of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotics prophylaxis is not recommended by either the 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*

In addition to patient risk factors, particular chemotherapy regimens are associated with an increased risk of FN and this must be considered when evaluating the patient's overall risk level. Regimens were categorised according to the proportion of patients that developed FN in published trials. Thresholds for these categories were >20%, 10–20% and <10%, these data are summarised in Table 4, and more detailed information is available in Appendix 5. For further discussion of FN risk, please see recommendation 4 below.

The identified trials generally focused on the results of overall therapy rather than FN incidence. As such, definitions of FN varied and the data may suffer from underreporting of febrile events, which is common in randomised controlled trials.[51] In addition, diverse FN rates were sometimes reported with the same chemotherapy regimens, something that could be attributable to 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 was unclear if this was the case, and therefore no specific analysis was possible. Nevertheless, it was clear that certain regimens in common usage are associated with the development of FN and FN-related complications.

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 4.

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.

Table 3 – Patient-related fisk factors for febrile neutropenia

	Lyman [21]	Timmer-Bonte [6]	Tjan-Heijnen [47]	Fosså [46]	Millward [44]	Gianni [45]	Lyman and Delgado [4]	Brooks [50]	Dale [51]
Cancer	Various	SCLC	SCLC	Germ cell tumours	NSCLC	Breast cancer	NHL	NHL	NHL
Study design	Systematic review	Phase III RCT	Phase III RCT	Phase III RCT	Phase II NR	Phase I NR	Retrospective	HE analysis	Retrospective
Patient risk factor									
Older age	III+	II +	I +	II +			IV +		IV+
Advanced disease/metastasis			I +			IV +	IV −	IV +	
No antibiotic prophylaxis			I +						
Prior episode of FN		II +							
No G-CSF use		II +					IV −		
Female gender	III+						IV +		IV+
Haemoglobin <12 g/dL/anaemia	III+ (FN in 1st cycle)							IV +	
Cardiovascular disease	III+ (NHL)						IV −		
Renal disease	III+ (NHL)	Excluded							
Abnormal liver transaminases	III+ (NHL)	Excluded				IV +			
Planned high (⩾80%) chemotherapy dose intensity	III+						IV +		
Poor performance and/or nutritional status	III+								IV+
⩾1 comorbidity							IV +	IV +	
Lymphoma histology								IV +	
Asian origin					IV +				
Body surface area <2.0 m^2							IV +		
Pretreatment ANC <1.5 × 10^9/L							IV +		
Serum albumin ⩽3.5 g/dL							IV +		

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

Table 4 – 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[19,54,55]	5–25
		Paclitaxel → AC[54]	40
		Doxorubicin/docetaxel[56,57]	33–48
		Doxorubicin/paclitaxel[19,45,58]	21–32
		TAC[19,59,60]	21–24
		DD/DDG FEC[61]	71/59
		DDG[c] doxorubicin → paclitaxel → cyclophosphamide[62]	2
		DDG[c] doxorubicin/cyclophosphamide → paclitaxel[62]	2
		DDG epirubicin/cyclophosphamide[63]	8
	10–20	AC[b19]	10–20
		Doxorubicin/vinorelbine[64]	15
		Docetaxel[5,19,65]	16–17
		Capecitabine/docetaxel[19,65]	13
		Cyclophosphamide/mitoxantrone[66]	11
		Epidoxorubicin/cyclophosphamide[a67]	13
		CEF[63]	14
		FEC 120[63,68]	9–14
	<10	FEC 90/100[69,70]	0–2
		CMF[71,72]	0–3
		CMF oral[68]	1
		Doxorubicin/cyclophosphamide[66]	2
		Doxorubicin → paclitaxel → cyclophosphamide[62]	3
		Doxorubicin/cyclophosphamide → paclitaxel[62]	5
		FAC 50[73]	5
		Epirubicin/cyclophosphamide ± lonidamide[74]	7
Small cell lung cancer	>20	ACE[6,19,47,75–78]	24–57
		Topotecan[a19,79]	28
		Topotecan/paclitaxel[19]	>20
		ICE[80]	24
		VICE[81]	70
		DDG[c] ACE[47,77]	34–56
		DDG[c] ICE[80]	18
		DDG[c] CAV → PE[82]	4
	10–20	CAV[83]	14
		Etoposide/carboplatin[19]	10–20
		Topotecan/cisplatin[19,137]	19
		CODE[84]	19
	<10	CAV → PE[82,84]	3–9
		Paclitaxel/carboplatin[85]	9
Non-small cell lung cancer	>20	Docetaxel/carboplatin[19,44]	26
		Etoposide/cisplatin[a86]	54
		VIG[19,87]	25
	10–20	Paclitaxel/cisplatin[19,88]	16
		Docetaxel/cisplatin[88,89]	5–11
		Vinorelbine/cisplatin[90,91]	1–10
	<10	Paclitaxel/carboplatin[88,92,93]	0–9
		Gemcitabine/cisplatin[94,95]	1–7
		Gemcitabine/cisplatin[88]	4
Non-Hodgkins lymphoma	>20	DHAP[19,96]	48
		ESHAP[19,97–99]	30–64
		CHOP-21[4,100]	17–50
		DD/DDG[c] VAPEC-B[19,101]	44/23
		DD/DDG[c] ACVBP[19,102]	78/52
	10–20	ACOD[19,103]	11
		R-CHOP-21[4,19]	19
		Fludarabine/mitoxantrone[19,104]	11
Ovarian cancer	>20	Docetaxel[19,105]	33
		Paclitaxel[a19,106]	22
	10–20	Topotecan[19,107,108]	10–18

Table 4 – *continued*

Malignancy	FN risk category (%)	Chemotherapy regimen and reference	FN risk
	<10	Paclitaxel/carboplatin[110,111]	3–8
		Gemcitabine/cisplatin[112]	9
Urothelial cancer	>20	Paclitaxel/carboplatin[113]	25
		MVAC[114]	26
		DDG[c] MVAC[114]	10
Germ cell tumours	>20	BOP → VIP-B[46]	46
		VeIP[19,115]	67
	10–20	Cisplatin/etoposide[19,116]	10
		BEP → EP[46]	13
Colorectal cancer	10–20	5-FU/leucovorin[117–119]	1–15
		FOLFIRI[120,121]	3–14
	<10	FOLFOX[122,123]	0–8
		IFL[118,119]	3–7
		Irinotecan[124,125]	2–7
Other malignancies	>20	TIC (head and neck cancers)[19,126]	30
		MAID (sarcoma)[19,127]	58
		Paclitaxel/cisplatin (cervical cancer)[19,128]	28
	10–20	Gemcitabine/irinotecan (pancreatic cancer)[19,92]	17
		Stanford V (Hodgkin's lymphoma)[129]	14
	<10	ABVD (Hodgkin's lymphoma)[129]	4
		Doxorubicin/cisplatin (endometrial cancer)[130]	2
		TAP (endometrial cancer)[130]	3

Please note that these results may vary for similar regimens depending on the patient population who participated in each study.
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; 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; CEF, cyclophosphamide/epirubicin/5-FU; CHOP-21, cyclophosphamide/doxorubicin/vincristine/prednisone; CMF, cyclophosphamide/methotrexate/fluorouracil; CODE, cisplatin/ vincristine/doxorubicin/etoposide; DD, dose dense; DDG, dose dense with G-CSF; DHAP, cisplatin/cytarabine/dexamethasone; ESHAP, etoposide/methylprednisolone/cytarabine/cisplatin; FAC, fluorouracil/doxorubicin/cyclophosphamide; FEC, cyclophosphamide/epirubicin/fluorouracil; FMD, fludarabine/mitoxantrone; FOLFIRI, 5-FU/l-folinic acid/d,l-folinic acid/irinotecan; FOLFOX, 5-FU/folinic acid/oxaliplatin; FN, febrile neutropenia; ICE, ifosfamide/carboplatin/etoposide; IFL, irinotecan/5-FU/calcium folinate; MAID, mesna/doxorubicin/ifosfamide/dacarbazine; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; PE, cisplatin/etoposide; Q2W, once every 2 weeks; R-CHOP-21, rituximab/CHOP; Stanford V, mustard/doxorubicin/vinblastine/vincristine/bleomycin/etoposide/predniso lone; T → AC, docetaxel followed by doxorubicin/cyclophosphamide; TAC, docetaxel/doxorubicin/cyclophosphamide; TAP, paclitaxel;oxorubicin/cisplatin; TIC, paclitaxel/ifosfamide/carboplatin; VAPEC-B, vincristine/doxorubicin/ prednisolone/etoposide/cyclophosphamide/bleomycin; VICE, vincristine/ifosfamide/carboplatin/etoposide; VIG, vinorelbine/ifosfamide/gemcitabine.
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. For further details, please see Appendix 5.

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

G-CSF to support intensive chemotherapy regimens. Dose-dense or -intense chemotherapy is increasingly used in an attempt to improve long-term clinical outcomes. Evidence has recently emerged, demonstrating that G-CSF prophylaxis can support the delivery of certain intensive chemotherapy regimens, by preventing any concomitant increase in the incidence of prolonged neutropenia or FN. Most of the relevant studies identified (14 of 16 in total) support the use of prophylactic G-CSF to enable the delivery of dose-dense or -intense chemotherapy and details of these studies are shown in Table 5.

In two level II studies where G-CSF was used to support dose-dense or -intense chemotherapy, the incidence of FN was higher in the dose-dense or -intense arms compared with the standard dose chemotherapy arms.[77,84] These studies offer a word of caution that for some patients, the use of prophylactic G-CSF support does not completely abolish the increased risk of FN associated with intensive chemotherapy.

Based on the evidence described above, we now recommend that in circumstances where dose-dense or dose-intense chemotherapy strategies have survival benefits,

Table 5 – Intensive chemotherapy regimens supported by G-CSF

Malignancy	Chemotherapy regimen and level of evidence		Reference
Dose dense regimens (increased frequency)[a]			
Breast cancer	FEC	I	Capotorto et al. [133]
	Epirubicin/cyclophosphamide		Therasse et al. [63]
	Doxorubicin → paclitaxel → cyclophosphamide		Citron et al. [62]
	Doxorubicin/cyclophosphamide → paclitaxel		Citron et al. [62]
	MMM	III	Capotorto et al. [133]
NHL	R-CHOP	II	Pfreundschuh et al. [41] Sonneveld et al. [40]
SCLC	ACE	II	Ardizzoni et al. [77]; Thatcher et al. [38]
	CAV → PE (alternating weekly)		Masutani et al. [82]
	VICE (⩾Q2W, not fixed)		Woll et al. [81]
	CODE (QW)		Furuse et al. [84]
	Cisplatin/epirubicin/paclitaxel		Frasci et al. [134]
NSCLC	Cisplatin/vindesine/mitomycin C (PVM)	II	Masutani et al. [135]
Urothelial cancer	MVAC	II	Sternberg et al. [114]
Dose intense regimens (increased dose)			
HD	BEACOPP	II	Diehl et al. [136]
Ovarian cancer	Paclitaxel	II	Omura et al. [106]
SCLC	ACE	II	Ardizzoni et al. [77]
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	Therasse et al. [63]
	Cyclophosphamide with high-dose mitoxantrone and withdrawal of doxorubicin	III	Fumoleau et al. [66]

5-FU = 5-flourouracil; ACE, doxorubicin/cyclophosphamide/etoposide; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazin e/prednisone; CAV → PE, cyclophosphamide/ doxorubicin/vincristine followed by cisplatin/etoposide; CODE, cisplatin/vincristine/doxorubicin/etoposide; 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; PVM, cisplatin/vindesine/mitomycin C; Q2W, once every 2 weeks; QW, once per week; SCLC, small cell lung cancer; VICE, vincristine/ifosfamide/carboplatin/etoposide.

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

prophylactic G-CSF should be given as a supportive treatment. Much of this evidence was recently obtained, and was published within the previous 5 years. For this reason, our recommendation differs from the previous ASCO guideline recommendation,[10] which was formulated before publication of these data.

G-CSF to maintain the dose intensity and/or dose density. Maintaining dose intensity may be particularly relevant when the treatment intent is curative or to prolong survival. There is strong and consistent evidence to show that G-CSF prophylaxis can be used to maintain chemotherapy at the desired dose intensity or density and to minimise delays. These findings are in agreement with those of ASCO,[10] EORTC[42] and NCCN.[19]

Almost all studies (12 of 13 identified) support the use of G-CSF in this context. There was evidence from three level I studies, that prophylaxis with G-CSF reduces the requirement for chemotherapy dose reductions.[113,138,139] Similarly, delays in chemotherapy treatment were reduced with G-CSF prophylaxis in three level I studies.[138–140] Finally, maintenance of chemotherapy dose intensity/density was significantly improved with G-CSF prophylaxis in seven level II studies.[1,6,46,82,102,135,141]. This was also the case in one level I study,[142] although the authors concluded that the improvements in dose density/intensity were not clinically relevant. It should be noted that the meta-analysis by Bohlius and colleagues included two studies of GM-CSF prophylaxis in addition to 10 studies where G-CSF was used.

In contrast, one level II study showed that the addition of varying intensity schedules of open-label G-CSF to high-dose epirubicin/cyclophosphamide chemotherapy in patients with stage I–II breast cancer, did not significantly improve an already high relative dose intensity.[74] However, it should be noted that the achieved dose intensity was 95% of planned in patients who did not receive G-CSF prophylaxis and 98% of planned in G-CSF-treated patients that received this low risk regimen.

The use of G-CSF to improve survival. While G-CSF support allows the use of intensive chemotherapy regimens that may improve survival, most of the reviewed evidence indicated that G-CSF prophylaxis on its own has no significant effect on overall or progression-free survival, as indicated by the relevant EORTC guidelines for elderly patients.[42] Two level I studies[139,142] and six level II studies[68,74,76,78,143] found no evidence to indicate that haematopoietic growth factors significantly improve overall, disease- or progression-free survival, compared with chemotherapy alone.

In contrast, one level II study found a significant survival advantage when dose-intense ACE was given with G-CSF support, compared to standard ACE alone.[38] In this study survival rates with and without G-CSF were 47% and 39%, respectively,

at 12 months and 13% and 8%, respectively, at 24 months ($P = 0.04$; 95% confidence intervals [CI] 0.65–0.99). Similarly, 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 to CHOP alone (62 of 104 patients died; $P = 0.045$).[100] Finally, a small level II study ($n = 65$) showed a tendency for improved long-term survival in patients with favourable-prognosis SCLC receiving VICE chemotherapy plus G-CSF compared with chemotherapy alone (2-year survival rate: 32% [95%CI 16–48%] vs. 15% [95%CI 2–27%], respectively), although the difference was not tested statistically.[81]

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. 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. Where this is not crucial, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered.

Recommendation grade A.

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

There is 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 four level I studies including two meta-analyses,[138,142] and two recent randomised, double-blind, phase III studies.[5,6] In the lymphoma study, the underlying FN risk was approximately 60% and relative risk (RR) reduction with G-CSF was approximately 25%.[142] In a review of solid tumours, the underlying FN risk was approximately 50% and relative risk reduction with G-CSF was approximately 50%,[138] and in a breast cancer study the underlying FN risk was approximately 17% and relative risk reduction with G-CSF was approximately 90%.[5] It should be noted that while the meta-analyses supported the use of G-CSF to reduce FN, some individual studies did not, and that pegfilgrastim was used in the study by Vogel and colleagues. Additional evidence in favour of G-CSF prophylaxis was found in five level II studies.[74,127,141,143,144] Conversely, in one level III study, the provision of G-CSF prophylaxis at $\leqslant 10$ μg/kg did not produce a significant reduction in the incidence of FN.[106]

When examining the evidence, it was clear that patients scheduled to receive certain chemotherapy regimens experience the most significant benefit from G-CSF prophylaxis. Two level I studies demonstrated a significant reduction in the incidence of FN, when patients received a chemotherapy regimen associated with FN in >40% patients.[138,142] Another level I study[6] and one level IV study,[145] found a significant reduction in FN incidence when patients received a chemotherapy regimen associated with FN in 20–40% 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.[31] In addition, one recent, large-scale level I study found that the provision of G-CSF prophylaxis produced a significant reduction in FN and FN-related complications, for patients who received chemotherapy associated with FN in 10–20% patients.[5]

Previous guideline recommendations have advocated that G-CSF should not be given unless a chemotherapy regimen associated with FN in >40% patients was to be used.[10,146] These recommendations were based on clinical data and economic models available at the time. However, there is now evidence to show that the prophylactic use of G-CSF in patients receiving chemotherapy associated with FN in >20% patients, significantly reduces the incidence of FN. In addition, 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. It is important that each of these factors is 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, it 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 is important for the reader to note that these are not designed to supersede nationally focussed guidelines, available in many cases.[147] Although an analysis of North American patients demonstrated the cost-effectiveness of G-CSF for patients at >20% risk of FN,[148–151] further data are needed and calculations should take into account all direct and indirect costs for each country and/or region. Please note that the current review did not include evidence derived from economic models.

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. 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)****. If the patient is at* $\geqslant$*20% overall risk of FN, prophylactic G-CSF is recommended. When using 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

The evidence to support the use of G-CSF to reduce the incidence of infection-related mortality is mixed. When used prophylactically, there are levels I and II evidence that G-CSF does not have a beneficial effect on infection-related mortality.[6,138,139,142]

However, there was level I 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 was a marginal but statistically significant improvement in FN-related events compared with standard treatment alone.[34] 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 colony-stimulating factor use on this outcome. It should be noted that the infection-related mortality rate in the control groups was low in all of the papers identified, which will result in a lack of power to detect a treatment effect. As mortality is generally very low in clinical trials, more informative data might be obtained if one were to examine the impact of G-CSF prophylaxis or treatment on infection-related mortality rates in a 'real-life' setting.

Our findings and recommendations are similar to those of ASCO,[10] which 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. A scoring system has been developed to aid the identification of patients at high risk of infection-related complications.[152]

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

Treatment with G-CSF for patients with solid tumours 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 infections (such as severe sepsis or septic shock).

Recommendation grade B.

3.11. Commentary on recommendation 6: Choice of formulation

Ten relevant reports were identified that addressed the use of different haematopoietic growth factors for the prevention or treatment of chemotherapy-induced FN.[29,31,34,48,60,67,138,142,153,154]

There is evidence from one level I,[34] two level II[48,67] and one level III[142] studies indicating that non-pegylated 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 endpoints.[138] 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.

Four studies compared prophylactic administration of the long-acting pegylated G-CSF, pegfilgrastim, with filgrastim.[29,31,153,154] In two small phase II trials (both evidence level III), filgrastim and pegfilgrastim were shown to have similar efficacy against FN-related endpoints, although underpowered to detect a treatment advantage.[153,154] Data from two phase III, multicentre, double-blind, randomised trials showed a lower incidence of FN in patients given pegfilgrastim compared to filgrastim,[29,31] although in one case this difference was not statistically significant. In these studies, the efficacy and safety of a single pegfilgrastim dose were compared with daily filgrastim in 157[29] and 310[31] 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 vs. filgrastim was 13% vs. 20% and 9% vs. 18%, respectively. Without G-CSF support, the AT regimen has been reported to be associated with an FN rate of 38%.[155]

A recently reported non-randomised study[60] showed a significantly lower FN rate amongst patients treated with pegfilgrastim, compared to those that received filgrastim (6% vs. 17%; $P < 0.001$). There was a further significant reduction in FN rate when patients received antimicrobial prophylaxis with pegfilgrastim, compared to pegfilgrastim or antimicrobial prophylaxis alone. Publication of further details of these data are awaited. While additional efficacy may be achieved with pegfilgrastim, this requires further clarification and there are few clinically important differences between the three agents.

3.12. Recommendation 6: Choice of formulation

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.

Recommendation grade A.

4. Conclusion

In conclusion, this review has produced some interesting and important findings, and has identified recent advances in the knowledge of G-CSF therapy. This has enabled us to produce up to date recommendations that are relevant to current European clinical practice. These may be used to optimise local protocols and patient management strategies in hospitals across Europe and, in turn, improve patient care and clinical outcomes. A summary of these guidelines can be found in Fig. 1.

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 their own independent clinical judgement and experience to determine appropriate care and treatment for their patients. The EORTC makes no guarantees of any kind in respect of the use or application of these guidelines and disclaims any liability for their application or use in any way.

Conflict of interest statement

Matti S. Aapro has received grants from, and serves on an advisory board and Speaker's Bureau for Amgen, Roche and sanofi-aventis. Julia Bohlius has received a lecture honorarium and travel grant from Amgen. David A. Cameron has received a travel grant from Amgen, honoraria from Amgen, Chugai and sanofi-aventis and research funding from Amgen.

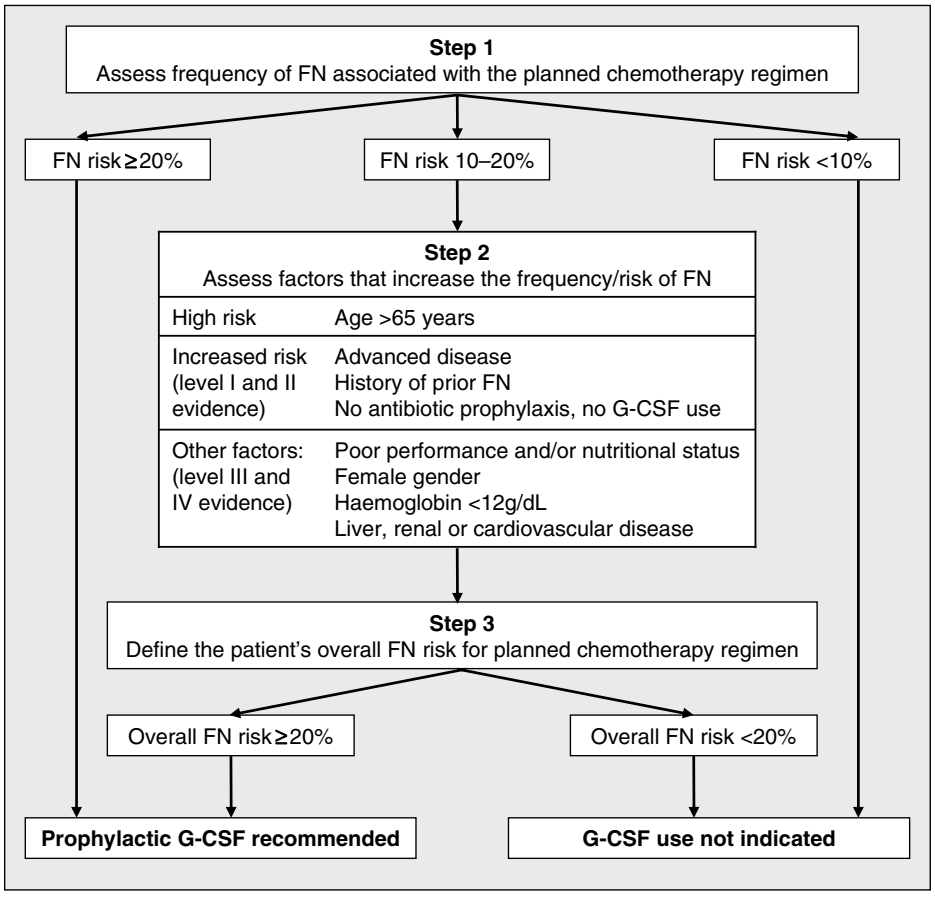

Fig. 1 – Patient assessment algorithm to decide prophylactic G-CSF usage.

Jeffrey Crawford has received research funding from, and serves on an advisory board for, Amgen. Nora Kearney has received honoraria from Amgen. Gary H. Lyman has received research funding from, and serves on a Speaker's Bureau for, Amgen. Ruth Pettengell has received honoraria and research funding from Amgen. Vivianne C. Tjan-Heijnen has received research funding from Amgen and sanofi-aventis. Jan Walewski has received a lecture honorarium and travel grant from Amgen. Christoph Zielinski has received an advisory board honorarium from Amgen and research funding and travel grants from sanofi-aventis. Michael Ellis and Damien Weber have no conflicts of interest in this work.

Table A1 – questions applied by the EORTC G-CSF guidelines working party

In adult cancer patients receiving chemotherapy:	
1.	Is there evidence that patient-related factors increase the risk of FN?
2.	Is there evidence that certain chemotherapy regimens increase the risk of FN?
3.	Is there evidence that some patients are more at risk of severe morbidity as a result of a FN episode?
4.	Is there evidence to support the use of G-CSF when there is a 20% risk level for FN?
5.	Is there evidence to support the use of G-CSF to: (a) maintain the correct dose of chemotherapy and relative dose intensity/density? (b) improve overall and progression-free survival?
6.	Is there evidence to support the use of G-CSF to enable the delivery of dose-dense/intense chemotherapy (a) by increasing the dose? (b) by withdrawing one drug and increasing the dose of the remaining drugs? (c) by increasing the dose frequency?
7.	Is there evidence to support the use of G-CSF to reduce the risk of infection-related mortality?
8.	Is there evidence to support the use of G-CSF to reduce the incidence of FN?
9.	Is there evidence to support the use of G-CSF for the treatment of ongoing FN?
10.	Is there evidence to support the use of different G-CSFs?

Table A2 – search terms used to interrogate electronic databases and meeting abstracts

Resource or database interrogated	MEDLINE, PreMEDLINE, EMBASE, The Cochrane Library	ASCO, ASH, AACR, EHA, ESMO, ECCO
Search terms[a]	Filgrastim, granulocyte colony-stimulating factor, haematological diseases, lenograstim, lymphoma, neoplasms (abdominal, anal gland, bone, breast, digestive system, endocrine gland, eye, head and neck, haematological, nervous system, pelvic, skin, soft tissue, splenic, thoracic, urogenital), Neulasta, Neupogen and pegfilgrastim	Filgrastim, G-CSF, granulocyte colony-stimulating factor, lenograstim, Neulasta, Neupogen, neutropenia and pegfilgrastim
Search strategy	Search 1: neupogen OR lenograstim OR filgrastim OR G-CSF OR "granulocyte colony stimulating factor" OR pegfilgrastim OR neulasta. Field: Title/Abstract Search 2: "abdominal Neoplasms"[MeSH] OR "Anal Gland Neoplasms"[MeSH] OR "Bone Neoplasms"[MeSH] OR "Breast Neoplasms"[MeSH] OR "Digestive System Neoplasms"[MeSH] OR "Endocrine Gland Neoplasms"[MeSH] OR "Eye Neoplasms"[MeSH] OR "Head and Neck Neoplasms"[MeSH] OR "Nervous System Neoplasms" [MeSH] OR "Pelvic Neoplasms"[MeSH] OR "Skin Neoplasms"[MeSH] OR "Soft Tissue Neoplasms"[MeSH] OR "Splenic Neoplasms"[MeSH OR "Thoracic Neoplasms"[MeSH] OR "Urogenital Neoplasms"[MeSH]. Search 3: "Hematological Neoplasms"[MeSH] OR "Hematological Diseases"[MeSH] OR "Leukemia"[MeSH] OR "Lymphoma"[MeSH]. Search 4: Search 2 NOT Search 3 Studies identified by the following searches were included: 1 AND 4; 1 AND 3; 1 NOT 3 NOT 4. All searches were limited by publication date and human studies. The searches were limited to meta-analyses or phase III studies by two methods, to ensure that all relevant studies were included. 1. Searches were limited to those tagged as either meta-analyses or Phase III studies within the relevant database. 2. Searches were limited to those tagged as 'clinical trials' and were manually searched for meta-analyses and Phase III studies.	

Abbreviations: American Society of Clinical Oncology [ASCO], American Society of Hematology [ASH], American Association for Cancer Research [AACR], European Hematology Association [EHA], European Society of Medical Oncology [ESMO] and The European Cancer Conference [ECCO].

a Please note that the brand names of lenograstim, neutrogin and granocyte, were not included in the search. However, a search for 'neutrogin' did not produce any results. A search for 'granocyte' identified 179 studies, all but five of which were excluded according to the criteria given in this appendix. Of the remaining five studies, all had been previously identified by other searches.

Table A3 – Number of papers of each evidence level included in the literature review

Recommendation		1	2	3					4		5		6
Question		Q1	Q2	Q5a	Q5b	Q6a	Q6b	Q6c	Q4	Q8	Q7	Q9	Q10
Level of positive evidence	I+	1	6	5	–	–	1	3	2	4	1	1	2
	II+	3	20	7	2	2	–	7	–	5	–	–	–
	III+	1	21	3	–	–	1	–	–	8	–	–	1
	IV+	5	–	2	–	–	–	1	1	1	–	–	–
Level of negative evidence	I–	–	1	–	2	–	–	–	–	–	2	–	1
	II–	1	1	1	6	1	–	2	–	–	2	–	3
	III–	–	1	–	–	–	–	–	–	1	–	–	3
	IV–	–	–	–	–	–	–	–	–	–	–	–	–
Total		11	50	18	10	3	2	13	3	19	5	1	10

Table A4 – Number of each study type included in the literature review

Recommendation	R1	R2	R3					R4		R5		R6
Question	Q1	Q2	Q5a	Q5b	Q6a	Q6b	Q6c	Q4	Q8	Q7	Q9	Q10
Phase I trial	–	–	–	–	–	–	–	–	–	–	–	–
Phase I/II trial	–	1	1	–	–	–	–	–	1	–	–	–
Phase II trial	1	13	4	1	–	–	1	–	1	–	–	2
Phase II/III trial	–	3	–	–	–	–	1	–	1	–	–	1
Phase III trial	5	18	6	2	3	2	7	1	6	2	–	3
Retrospective observational study	3	1	3	–	–	–	–	1	2	–	–	–
Meta-analysis	–	–	2	–	–	–	–	–	1	2	1	2
Systematic review	1	–	1	1	–	–	–	–	2	1	–	1
Not reported	1	14	1	6	–	–	4	1	5	–	–	1
Total	11	50	18	10	3	2	13	3	19	5	1	10

In total 71 pieces of evidence were included, of which 53 were identified by the electronic database search or meta-analysis review. The congress abstract review identified 6 further studies, of which 3 were full publications and 3 were posters or presentations. An additional 12 papers not identified by these searches, were highlighted by members of the working party as being relevant to particular questions.

Table A5 – Risk of febrile neutropenia associated with common chemotherapy regimens

Chemotherapy	Dose (mg/m^2, unless otherwise stated) and dosing schedule	Risk of FN (%)
Breast cancer		
FEC 90/100[69,70]	500/90–100/500 Q3W	0–2
CMF[71,72]	600/(40/600)$^{d1+8}$ Q3W	0–3
CMF oral[68]	100^{d1-14}/(40/600)$^{d1+8}$ Q4W	1
Doxorubicin/cyclophosphamide[66] (level III)	60/600 Q3W	2
DD doxorubicin → paclitaxel → cyclophosphamide[62] (level I)	(60 → 175 → 600) Q2W + G-CSF	2
DD doxorubicin/cyclophosphamide → paclitaxel[62] (level I)	(60/600 → 175) Q2W + G-CSF	2
Doxorubicin → paclitaxel → cyclophosphamide[62] (level I)	(60 → 175 → 600) Q3W	3
FAC 50[73]	500/50/500 Q3W	5
Doxorubicin/cyclophosphamide → paclitaxel[62] (level I)	(60/600 → 175) Q3W	5
AC → docetaxel[19,54,55] (level U/II/III)	(60/600 → 100) Q3W	5–25
Epirubicin/cyclophosphamide ± lonidamide[74] (level III)	120/600 ± 450mg/d Q3W	7
DD epirubicin/cyclophosphamide[63] (level I)	120/830 Q2W + G-CSF	8
FEC 120[63,68]	(500/60)$^{d1+8}$/75^{d1-14} Q4W	9–14
AC[19]	60/600 Q3W	10–20
Cyclophosphamide/mitoxantrone[66] (level III)	600/23 Q3W + G-CSF	11
Epidoxorubicin/cyclophosphamide[67] (level II)	100/600 Q2–3W	13
Capecitabine/docetaxel[19,65] (level U/II)	2,500^{d1-14}/75 Q3W	13
CEF[63] (level I)	75^{d1-14}/60^{d1+8}/500^{d1+8} Q4W	14
Doxorubicin/vinorelbine[64]	40/20^{d1+8} Q3W	15
Docetaxel[5,19,65] (level U/II/I)	100 Q3W	16–17
Doxorubicin/paclitaxel[19,45,58] (level U/III/U)	60/125–200 Q3W	21–32
TAC[19,59,60]	75/50/500 Q3W	24
Doxorubicin/docetaxel[56,57]	50/75 Q3W	33–48
T → AC[54] (level II)	(100 → 60/600) Q3W	40
DD FEC[61] (level II)	3,000^{d1-3}/35^{d2-4}/400^{d2-4} Q3W	71
Colorectal cancer		
FOLFOX[122,123]	Variations on standard	0–8
5-FU/leucovorin[117–119]	Various	1–15
IFL[118,119]	Various	3–7
Irinotecan[124,125]	300–350 Q3W or 125$^{d1+7+14+21}$	2–7
FOLFIRI[120,121]	Variations on standard Q2W	3–14
Pancreatic cancer		
Gemcitabine/irinotecan[19,92] (level U/III)	1,000^{d1+8}/300^{d8} Q3W	17
Non-small-cell lung cancer		
Paclitaxel/carboplatin[88,93,131] (level U/U/I)	175–225/AUC6 Q3W	0–9
Gemcitabine/cisplatin[94,95]	1,250^{d1+8}/75–100 Q3W	1–7

(*continued on next page*)

Table A5 – *continued*

Chemotherapy	Dose (mg/m^2, unless otherwise stated) and dosing schedule	Risk of FN (%)
Vinorelbine/cisplatin[90,91]	25/100 Q4W	1–10
Gemcitabine/cisplatin[88] (level I)	$1{,}000^{d1+8+15}$/100 Q4W	4
Docetaxel/cisplatin[88,89] (level U/I)	75/75 Q3W	5–11
Paclitaxel/cisplatin[19,88] (level U/I)	$135/75^{d2}$ Q3W	16
VIG[19,87]	$(25^{d1}$ + 20–$25^{d4})$/3,000/$(1{,}000^{d1}$ + 800–$1{,}000^{d4})$ Q3W	25
Docetaxel/carboplatin[19,44] (level U/III +)	75/AUC6 Q3W	26
Etoposide/cisplatin[86]	$(200/35)^{d1-3}$ Q4W	54
Small-cell lung cancer		
CAV → PE[82,84] (level II/II)	(800/50/1.4 → 80–100/100^{d1-3}) Q3W	3–9
DD CAV → PE[82] (level II)	(500/30/1 → 50/75^{d1+2}) QW	8
Paclitaxel/carboplatin[85]	200/AUC6 Q3W	9
Etoposide/carboplatin[19]	100^{d1-3}/300 Q3W	10–20
CAV[83]	750/40/1.3 Q3W	14
DD CE[80] (level II)	5,000/300/180^{d1+2} Q2W + G-CSF	18
CODE[84] (level II)	$25/1^{(\text{not W3,5,7}-9)}/40^{(\text{not W2,4,6,8})}/80^{d1-3(\text{not W2,4,6,8})}$ QW + G-CSF	19
Topotecan/cisplatin[19,77] (level U/III)	0.75^{d1-5}/60 Q3W	19
Topotecan/paclitaxel[19]	$1^{d1-5}/135^{d5}$ Q4W	>20
ICE[80] (level II)	5,000/300/180^{d1+2} Q4W	24
ACE[6,19,47,75–78] (level U/U/I/II/I/II/II)	45–50/1,000/100–120^{d1-3} Q3W	24–57
Topotecan[19,79]	1.5^{d1-5} Q3W	28
DD ACE[47,77] (level II/I)	55/1,250/125^{d1-3} Q2W + G-CSF	34–56
VICE[81] (level II)	$1mg^{d15}$/5,000/300/120^{d1+2}+240^{d3} Q2–6W	70
Ovarian cancer		
Paclitaxel/carboplatin[110,111]	175–185/AUC5–6 Q3W	3–8
Gemcitabine/cisplatin[112]	$1{,}000^{d1+8}$/AUC5 Q3W	9
Topotecan[19,107–109] (level U/U/U/III)	1.5^{d1-5} Q3W	10–18
Paclitaxel[19,106] (level U/II)	135–175 Q3W	22
Docetaxel[19,105] (level U/III)	75–100 Q3W	33
Cervical cancer		
Paclitaxel/cisplatin[19,128] (level U/III)	$135–170/75^{d2}$ Q3W	28
Endometrial cancer		
Doxorubicin/cisplatin[130] (level III)	60/50 Q3W	2
TAP[130]	160d2/45/50 + G-CSF Q3W	3
Urothelial cancer		
DD MVAC[114] (level II)	$30^{d1+8}/3^{d1+8}/30^{d2}$/70 + G-CSF Q2W	10
Paclitaxel/carboplatin[113] (level III)	150–225/AUC6 Q3W	25
MVAC[114] (level II)	$30^{d1+8+15}/3^{d1+8+15}/30^{d2}$/70 Q4W	26
Germ cell tumours		
Cisplatin/etoposide[19,116] (level U/III)	$(20/100)^{d1-5}$ Q3W	10
BEP → EP[46] (level II)	$30U^{d2+9+16}/100^{d1-5}/20^{d1-5}$ Q3W → $100^{d1-5}/20^{d1-5}$ Q3W	13
BOP → VIP-B[46] (level II)	$30U/2mg/50^{d1+2}$ Q10d → $20^{d1-5}/1{,}000^{d1-5}/100^{d1+3+5}/30U^{d8+15}$ Q3W	46
VeIP[19,115] (level U/III)	$0.11mg/kg^{d1+2}/1{,}200^{d1-5}/20^{d1-5}$ Q3W	67
Head and neck cancer		
TIC[19,126] (level U/III)	$175/1{,}000^{d1-3}$/AUC6 Q3–4W	30
Sarcoma		
MAID[19,127] (level U/II)	$(3{,}000/20/2{,}500/300)^{d1-3}$ Q3W	58
Hodgkin's disease		
ABVD[129]	$(25/10/6/375)^{d1+15}$ Q4W	4
Stanford V[19,132] (level U/III)	Standard	14
Non-Hodgkin's lymphoma		
ACOD[19,103]	$25/500/1.2^{d1+8}/50\ mg^{d1+8}$ Q3W	11
Fludarabine/mitoxantrone[19,104] (level U/III)	25^{d1-3}/10 Q4W	11
CHOP-21[4,100] (level II/U)	$750/50/1.4/50–100\ mg^{d1-5}$ Q3W	17–50
R-CHOP-21[4,19]	$375/(750/50/1.4)^{d3}/\ 100\ mg^{d3-7}$ Q3W	19
ESHAP[19,97–99] (level U/U/U/III)	$40–60^{d1-4}/500\ mg^{d1-5}/\ 2{,}000^{d5}/25^{d1-4}$ Q3W–Q4W	30–64
VAPEC-B[19,101] (level U/II)	$1.4/35/0–50\ mg^{d1-7}/100^{d1-5}$/350/10 QW	44
DHAP[19,96]	$100/2$ x $2{,}000^{d2}/40\ mg^{d1-4}$ Q3W–Q4W	48
A(N)CVB[19,102] (level U/II)	$75(12)/1{,}200/2^{d1+5}/10\ mg^{d1+5}$ Q2W	78

Table A5 – *continued*

These results may vary for similar regimens depending on the patient population who participated in each study.
5-FU = 5-fluorouracil; AC = doxorubicin/cyclophosphamide; ABVD = doxorubicin/bleomycin/vinblastine/dacarbazine; AC → T = doxorubicin/cyclophosphamide followed by docetaxel; ACE = doxorubicin/cyclophosphamide/etoposide; ACOD = doxorubicin/cyclophosphamide/vincristine/prednisolone; A(N)CVB = doxorubicin/mitoxantrone/cyclophosphamide/vindesine/bleomycin; AUC = area under the curve; BEP = bleomycin/etoposide/cisplatin; BOP = bleomycin/vincristine/cisplatin, CAV = cyclophosphamide/ doxorubicin/vincristine; CE = cyclophosphamide/epirubicin; CEF = cyclophosphamide/epirubicin/5-FU; CHOP-21 = cyclophosphamide/doxorubicin/vincristine/prednisone; CMF = cyclophosphamide/methotrexate/fluorouracil; CODE = cisplatin/ vincristine/doxorubicin/etoposide; [d] = day; DD = dose dense; DHAP = cisplatin/cytarabine/dexamethasone; EP = etoposide/cisplatin; ESHAP = etoposide/methylprednisolone/cytarabine/cisplatin; FAC = fluorouracil/doxorubicin/cyclophosphamide; FEC = cyclophosphamide/epirubicin/fluorouracil; FN = febrile neutropenia; FOLFIRI = 5-FU/l-folinic acid/d,l-folinic acid/irinotecan; FOLFOX = 5-FU/folinic acid/oxaliplatin; G–CSF = granulocyte–colony stimulating factor; ICE = ifosfamide/carboplatin/etoposide; IFL = irinotecan/5-FU/calcium folinate; MAID = mesna/doxorubicin/ifosfamide/dacarbazine; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin; PE = cisplatin/etoposide; Q10d = once every 10 days; QW = once weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q4W = once every 4 weeks; Q5W = once every 5 weeks; R-CHOP-21 = rituximab/CHOP; Stanford V = mustard/doxorubicin/vinblastine/vincristine/bleomycin/etoposide/prednisolone; T → AC = docetaxel followed by doxorubicin/cyclophosphamide; TAC = docetaxel/doxorubicin/cyclophosphamide; TAP = paclitaxel;oxorubicin/cisplatin; TIC = paclitaxel/ifosfamide/carboplatin; U = ungraded; VAPEC-B = vincristine/doxorubicin/prednisolone/etoposide/cyclophosphamide/bleomycin; VeIP = vinblastine/ifosfamide/cisplatin; VICE = vincristine/ifosfamide/carboplatin/etoposide; VIG = vinorelbine/ifosfamide/gemcitabine; VIP-B = cisplatin/ifosfamide/etoposide/bleomycin.

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Appendix 1. Questions applied by the EORTC G-CSF guidelines working party

See Table A1.

Appendix 2. Search terms used to interrogate electronic databases and meeting abstracts

See Table A2.

Appendix 3. Details of the additional literature search used in the formulation of Recommendation 2

For Question 2, it was clear that the search was not broad enough to capture all information on the risk of FN associated with certain chemotherapy regimens, as the identified studies were restricted to those that included G-CSF in their protocols. To supplement the data obtained in the search, an additional analysis was undertaken. An independent expert selected a range of common chemotherapy regimens – with respect to European practice – across five different solid tumour types (breast cancer, colorectal cancer, small cell lung cancer [SCLC], non-small cell lung cancer [NSCLC] and ovarian cancer) and two lymphomas (Hodgkin's disease [HD] and NHL) (Table 4). A computerised literature search of MEDLINE was then undertaken (19th May 2005) to identify phase III studies (and phase II studies, if phase III studies were lacking) in which these regimens were used in adult patients with the above malignancies. Identified papers were scanned to determine the FN rate (if reported) associated with the different chemotherapy regimens. Chemotherapy dose and dosing schedule were also noted. Evidence identified in both the initial and subsequent searches were used in the final data analysis. Search results were cross-checked against recent NCCN guidelines[19] to ensure consistency of results.

Appendix 4. General details of the evidence included in the literature review

See Tables A3 and A4.

Appendix 5. Risk of febrile neutropenia associated with common chemotherapy regimens

See Table A5.

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