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Position Paper

EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer

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Abstract

Increasing age is not, in itself, a contraindication to cancer chemotherapy. Myelosuppression, however, a common adverse consequence of the administration of many standard-dose chemotherapy regimens to both young and elderly patients with cancer, increases with age. The risk of development of febrile neutropenia may contribute to a reluctance to administer chemotherapy in the elderly patient population. We conducted a detailed literature search (1992–2002) to derive evidence-based conclusions on the value of prophylactic colony-stimulating factor (CSF) administration in elderly patients receiving chemotherapy. Sufficient evidence allows us to affirm that prophylactic granulocyte colony-stimulating factor (G-CSF) reduces the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy for non-Hodgkin's lymphoma (NHL), small-cell lung cancer (SCLC) or urothelial tumours. Lack of available trial data does not allow similar conclusions to be drawn for other cancers studied, but it is likely that similar benefits would accrue from the use of prophylactic G-CSF. There is insufficient evidence to extend this recommendation to include the use of granulocyte-macrophage colony-stimulating factor (GM-CSF). There are insufficient data available to allow the evaluation of the impact of prophylactic CSF on the incidence of toxic deaths in elderly patients with cancer and this is a crucial question for geriatric oncology practice. There is no evidence in elderly patients that the delivery of standard-dose chemotherapy on schedule improves efficacy measures. The data show that febrile neutropenic events are more likely to occur during the first and second cycles of chemotherapy, thus prophylactic measures should be considered early in the course of treatment. Furthermore, since systematic dose reduction can impact on outcome, primary prophylactic use of G-CSF for all elderly patients receiving curative myelotoxic chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or CHOP-like) is indicated and we suggest a risk-adapted strategy with primary prophylactic G-CSF administration in high-risk patients. Dose intensification, through dose interval reduction, facilitated by prophylactic G-CSF, improved survival in elderly patients with some specific diseases. There is a need for further well-designed studies to identify the elderly patients who will benefit most from prophylactic G-CSF. To achieve this, we strongly urge the design of and participation in further trials.

Keywords: Granulocyte colony-stimulating factor; Granulocyte-macrophage colony-stimulating factor; Aged; Neutropenia; Cancer; Treatment guidelines

1. Introduction

Increasing age is not, in itself, a contra-indication to cancer chemotherapy, but many clinicians are reluctant to use chemotherapy in elderly patients. Comprehensive geriatric assessment may enable clinical estimation of true life expectancy of the elderly patient and indicate the benefits of potentially curative or palliative chemotherapy [1]. However, whilst myelosuppression is a common adverse consequence of the administration of many standard-dose chemotherapy regimens in both young and elderly patients with cancer, increasing age is

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associated with increasing haematological toxicity [2–4], and is a significant independent predictor of the development of febrile neutropenia [5,6]. Consequently, the increased risk of myelosuppression may contribute to a reluctance to administer chemotherapy in the elderly patient population.

Chemotherapy dose reduction or delay is a strategy that is frequently employed to manage chemotherapy-induced neutropenia. However, reducing the chemotherapy dose or delaying administration may have a negative impact on outcomes. For example, several studies have shown that dose reductions of 20–30% are associated with lower complete response (CR) rates and/or survival in non-elderly patients with Non-Hodgkin's lymphoma (NHL) [7–9]. Similarly, in patients with breast cancer, Bonadonna and colleagues [10] found that sub optimal dose administration (<85% of planned) was associated with significantly reduced relapse-free and overall survival (OS). An alternative strategy to dose reduction or delay is to provide neutrophil support through the prophylactic use of haematopoietic growth factors. Whilst haematopoietic reserve may decline with advancing age [11], the response of elderly patients to exogenously administered granulocyte-colony stimulating factor (G-CSF) is maintained [12].

Haematopoietic growth factor administration has been recommended to provide cost-effective support of the first and subsequent cycles of chemotherapy in patients who have an expected incidence of febrile neutropenia $\geqslant$40% or who are at high risk of infectious complications (primary prophylaxis) and as secondary prophylaxis for the avoidance of further episodes of febrile neutropenia following an initial occurrence [13]. Whilst the incidence of febrile neutropenia cut-off point of $\geqslant$40% defines an intervention with growth factors that is expected to be cost-saving and their use in patients with an expected incidence of febrile neutropenia <40% may be associated with increased financial costs, significant improvements in quality of life may accrue. The National Cancer Center Network (NCCN, USA) has recommended that routine primary prophylactic growth factors should be used in patients aged $\geqslant$70 years who are receiving moderately myelotoxic chemotherapy of a comparable dose intensity to 21-day cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) [1]. The American Society of Clinical Oncology (ASCO) Committee on Guidelines for the use of Haematopoietic Growth Factors has concurred with the NCCN recommendation [14].

A Working Party on the use of Colony-Stimulating Factors in Elderly Patients was established by the European Organisation for Research and Treatment of Cancer (EORTC) Cancer in the Elderly Task Force. The objective of the research of our Working Party was to methodically review the existing published data and derive evidence-based conclusions on the value of prophylactic colony-stimulating factor (CSF) administration in elderly patients receiving chemotherapy for the treatment of a number of predefined malignant diseases.

2. Patients and methods

MEDLINE was chosen as a primary source of information due to its precise indexing and general availability. Electronic searches were conducted using the MEDLINE database for English language records from 1992 to March 2002. Search terms were used to extract data relating to each tumour type, G-CSF or granulocyte macrophage (GM)-CSF, and were limited to clinical trials in patients aged $\geqslant$60 years. This boundary for elderly had to be chosen in order to have sufficient data, even if the International Committee of Harmonization (ICH) Good Clinical Practice (GCP) boundary is 65 years. Studies were excluded if median age was <60 years and the proportion of patients aged $\geqslant$60 years was less than 25% with no age-specific sub analysis. Pre-MEDLINE was also searched for relevant recently published studies. Additionally, the abstract books from key international meetings were manually searched for relevant study reports.

Evidence levels used also by ASCO (Table 1) were applied to the results of our literature search to classify data according to study design. An EORTC Working Party reviewed the search findings and agreed which studies were relevant and sufficiently powered to address the questions described in Table 2. For each study, all of

Table 1
ASCO evidence levels

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 study
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

ASCO, American Society of Clinical Oncology.

Table 2
Questions applied by the EORTC expert panel

Toxicity and efficacy during standard dose chemotherapy	
a	Does G-CSF administration in elderly patients permit administration of chemotherapy at doses planned and on schedule?
b	Does G-CSF administration in elderly patients reduce chemotherapy-induced neutropenia?
c	Does G-CSF administration in elderly patients reduce febrile neutropenia?
d	Does G-CSF administration in elderly patients reduce infection rates?
e	Does G-CSF administration in elderly patients reduce toxic deaths?
f	Does G-CSF administration in elderly patients improve response rates?
g	Does G-CSF administration in elderly patients improve progression-free or disease-free survival?
h	Does G-CSF administration in elderly patients improve overall survival?
Feasibility and efficacy of intensified chemotherapy	
i	Is dose intensification feasible with growth factor prophylaxis?
j	Does dose intensification facilitated by growth factor administration in the elderly improve the response rate?
k	Does dose intensification facilitated by growth factor administration in the elderly improve progression-free or disease-free survival?
l	Does dose intensification facilitated by growth factor administration in the elderly improve overall survival?

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

the predefined questions in Table 2 were considered and positive or negative evidence was noted. This allowed grading of evidence (see footnote to Table 4) and subsequent development of recommendations to define the use, or otherwise, of prophylactic CSF administration.

We investigated seven tumour types; breast cancer, colorectal cancer, NHL, non-small cell lung cancer (NSCLC), ovarian cancer, small-cell lung cancer (SCLC) and urothelial cancer. Evidence obtained was categorised according to the type of CSF administered; G-CSF or GM-CSF. Studies describing the use of standard-dose chemotherapy were reviewed for both toxicity and efficacy evidence. However, since trials that utilised dose-intense chemotherapy regimens compared the toxicity of regimens of dissimilar intensity, such studies were appraised only for feasibility and efficacy.

3. Results

A total of 330 references were identified by the search strategy. Greater than 90% of the research identified by the search strategy was excluded during review (Table 3). The major reasons for exclusion were median age <60 years and a lack of direct comparison of growth factor versus no growth factor. In total, 30 papers provided

Table 3
A breakdown of the number of papers/abstracts identified within the search strategy and the number subsequently considered by the EORTC expert panel to contain applicable evidence

Disease state/G-CSF or GM-CSF	Number of papers identified by on-line search	Number of on-line papers that conform to inclusion criteria	Number of abstracts identified by manual search	Total number of references considered relevant by the expert panel
Breast cancer/G-CSF	71	0	2	0
Colorectal cancer/G-CSF	8	2	0	0
NHL/G-CSF	27	9	12	7
NSCLC/G-CSF	48	21	4	1
Ovarian cancer/G-CSF	44	6	1	2
SCLC/G-CSF	37	19	6	10
Urothelial cancer/G-CSF	15	11	0	4
Breast cancer/GM-CSF	17	0	0	0
Colorectal cancer/GM-CSF	16	1	0	0
NHL/GM-CSF	21	3	0	1
NSCLC/GM-CSF	7	2	0	1
Ovarian cancer/GM-CSF	5	0	0	0
SCLC/GM-CSF	13	5	0	4
Urothelial cancer/GM-CSF	1	0	1	0

EORTC, European Organisation for Research and Treatment of Cancer ;NHL, Non-Hodgkin's Lymphoma; SCLC, Small-cell lung cancer; NSCLC, Non-small cell lung cancer; GM-CSF, granulocyte macrophage-colony stimulating factor; G-CSF, granulocyte colony-stimulating factor.

Table 4
Level of evidence summary table (G-CSF)

Question[a]	Breast	Colorectal	NHL	NSCLC	Ovarian	SCLC	Urothelial
Toxicity and efficacy during standard-dose chemotherapy							
a	D	D	C	D	D	B	B
b	D	D	A[b]	D	D	A	B
c	D	D	D	D	D	A	B
d	D	D	A[b]	D	D	A	B
e	D	D	D	D	D	A−ve	D
f	D	D	A−ve	D	D	A−ve	D
g	D	D	A−ve	D	D	A−ve	D
h	D	D	A−ve	D	D	A−ve	D
Feasibility and efficacy of dose-intensified chemotherapy							
i	D	D	A[b]	D	B	A	C
j	D	D	A[b]	D	D	A−ve	D
k	D	D	D	D	D	D	B
l	D	D	A[b]	D	D	C	D

G-CSF, granulocyte colony-stimulating factor. −ve indicates that the evidence shows a negative recommendation; 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 generally inconsistent; D: there is little or no systematic empirical evidence.

[a] For definitions of questions, please see Table 2.

[b] Abstract evidence only.

evidence considered relevant by the EORTC panel. It is important to note that even in the studies in which mean patient age was $\geqslant 60$ years, there was little information regarding the proportion of these patients that were $\geqslant 70$ or $\geqslant 80$ years.

3.1. Breast cancer

Seventy-three published studies relating to the use of G-CSF in elderly patients with breast cancer were identified and, of these, all but two were excluded according to the previously defined criteria [15,16]. Neither paper provided any relevant evidence for the use of G-CSF in elderly patients with breast cancer.

Seventeen published studies were identified relating to the use of GM-CSF in elderly patients with breast cancer, but all were excluded according to the previously defined criteria.

3.2. Colorectal cancer

Eight published studies relating to the use of G-CSF and 16 relating to the use of GM-CSF in elderly patients with colorectal cancer were identified. None of the papers provided any relevant evidence for the use of G-CSF or GM-CSF in elderly patients with colorectal cancer.

3.3. NHL

Thirty-nine related papers were identified for G-CSF use in elderly NHL patients and, of these, all but 21 were excluded according to the previously defined criteria. Twenty-one published studies were identified relating to the use of GM-CSF in elderly patients with NHL and, of these, all but three were excluded according to the previously defined criteria.

One study in elderly patients with NHL provided Level I evidence that primary prophylactic G-CSF significantly improved the delivery of planned standard-dose chemotherapy [17]. There was, however, also conflicting Level I and II evidence [18,19]. There is Level I and II evidence that prophylactic G-CSF reduces the incidence of chemotherapy-induced neutropenia [18,19]. Two studies provided Level I evidence [17,18], and one study provided Level II evidence [19] that primary prophylactic G-CSF significantly reduced infection rates when compared with patients not receiving growth factor support. There was Level I and Level II evidence that response rates [17–19], progression-free survival (PFS) [17–19] and OS [17,19] were very similar irrespective of prophylactic G-CSF administration. Level I [20] and III [21,22] evidence indicates that chemotherapy dose intensification through dose interval reduction without excessive toxicity is feasible with primary prophylactic G-CSF. There is Level I evidence that patients receiving dose-intensified chemotherapy with primary prophylactic G-CSF support had a significantly improved response rate, freedom from treatment failure and OS when compared with patients receiving standard chemotherapy with no prophylactic growth factor support [20]. Two studies provided positive Level II evidence that primary or secondary prophylactic GM-CSF reduces the incidence or duration of chemotherapy-induced neutropenia [23,24] and one of these studies indicated that there was no impact on response rate or OS [23].

3.4. NSCLC

Fifty-two related studies were identified for the use of G-CSF in elderly patients with NSCLC and, of these, all but 25 were excluded according to the previously defined criteria. Seven published studies were identified relating to the use of GM-CSF in elderly patients with NSCLC and, of these, all but two were excluded according to previously defined criteria.

One study provided Level III evidence of a reduction in the incidence of chemotherapy-induced neutropenia and febrile neutropenia in patients receiving prophylactic G-CSF compared with prior cycles of chemotherapy with no G-CSF support and enabled dose intensification [25]. One study provided Level II evidence of a reduction in the incidence of chemotherapy-induced neutropenia in patients receiving prophylactic GM-CSF compared with patients receiving no GM-CSF support [26]. This did not impact on infection rates or response rates.

3.5. Ovarian cancer

Forty-five related papers were found relating to the use of G-CSF in elderly patients with ovarian cancer and, of these, all but seven were excluded according to previously defined criteria. Five papers were found relating to the use of GM-CSF in elderly patients with ovarian cancer, but all were excluded according to the previously defined criteria.

Two papers provided level III evidence that dose intensification of chemotherapy is possible in patients receiving prophylactic G-CSF [27,28]. No evidence was identified for the use of GM-CSF in elderly patients with ovarian cancer.

3.6. SCLC

Forty-three studies relating to the use of G-CSF in elderly patients with SCLC were identified by our search strategy and, of these, all but 25 were excluded according to the previously defined criteria. One further phase 3 randomised trial was identified by the expert panel as key evidence and was included in the results despite being published outside of the search strategy time limits [29]. Additionally, one further study including patients with a median age of 59 years was included in the results on the basis that this was a well-designed phase 3 study [30]. Thirteen published studies were identified relating to the use of GM-CSF in elderly patients with SCLC and, of these, all but five were excluded according to the previously defined criteria.

One study provided Level I evidence [30], and one Level II evidence [31] that prophylactic G-CSF significantly reduced the number of chemotherapy dose reductions when compared with patients not receiving growth factor. However, the results of these studies are in conflict with data published by Gatzemeier and colleagues (Level I) [32] and Miles and colleagues (Level II) [33]. There is Level I–IV evidence that chemotherapy-induced neutropenia was less frequent in patients receiving G-CSF prophylaxis when compared with patients treated with chemotherapy alone [29–31,33,34]. There is Level I [29,30] and Level II evidence [31] that prophylactic G-CSF significantly reduces the incidence of febrile neutropenia. Similarly, there is Level I evidence that prophylactic G-CSF significantly reduces infection rates when compared with patients not receiving growth factor support [29,32]. One study provided Level I evidence that prophylactic G-CSF had no impact on the incidence of toxic death [32].

There is Level I evidence that the administration of prophylactic G-CSF had no impact on response rates [29,30,32], PFS [29,32] or OS [29,30,32]. One study provided contradictory Level II evidence that prophylactic G-CSF significantly improved OS [31].

Dose intensification in elderly patients with SCLC is feasible with the prophylactic use of G-CSF as evidenced by Level I–III studies [34–37]. However, there is little evidence that this impacts on treatment outcomes. There is Level I [35,36], Level II [37] and Level IV evidence [34] that dose-intensification with G-CSF support does not improve response rates when compared with non-G-CSF-supported standard chemotherapy. Similarly, there is Level II evidence that dose-intensification has no impact on PFS [37]. Interestingly, Thatcher and colleagues [35] found a significant survival advantage in patients receiving dose-intensified chemotherapy with primary prophylactic G-CSF when compared with patients receiving standard chemotherapy. Similarly Woll and colleagues [37] found Level II evidence of an improved 2-year survival following dose-intensified chemotherapy with G-CSF prophylaxis when compared with standard chemotherapy. There was also conflicting Level I evidence indicating no impact of dose-intensification on survival [36].

There was conflicting Level I evidence [38,39] that prophylactic GM-CSF improved the scheduled delivery of planned chemotherapy. Three papers provided Level I evidence that patients randomised to GM-CSF did not have a significantly lower incidence of chemotherapy-induced neutropenia than those receiving no growth factor support [38–40]. Steward and colleagues reported Level I evidence that the incidence of febrile neutropenia was not affected by the prophylactic use of GM-CSF. Similarly, two studies provided Level I evidence that prophylactic GM-CSF does not reduce the incidence of infections following chemotherapy [38,40]. One study provided Level I evidence that patients randomised to GM-CSF had significantly more toxic deaths than patients receiving no cytokine support, but

this may be due to the concurrent application of radiotherapy [38]. There is Level I evidence that prophylactic GM-CSF has no impact on the response rate [39,40] or OS [38–40]. One paper provided Level II evidence that GM-CSF facilitated the delivery of accelerated chemotherapy with fewer treatment delays, shorter median treatment duration and higher dose intensity [41]. However, there is conflicting Level I evidence that GM-CSF prophylaxis does not facilitate dose-intensification [40]. Sculier and colleagues reported a positive impact of dose-intensification on the response rate, but not on OS, when compared with patients not receiving growth factor support.

3.7. Urothelial cancer

Fifteen published studies relating to the use of G-CSF in patients with urothelial cancer were identified and, of these, all but 11 were excluded according to the previously defined criteria. Two studies relating to the use of GM-CSF in patients with urothelial cancer were identified, but only one conformed to the inclusion criteria. There is Level II evidence that the prophylactic use of G-CSF in patients with urothelial tumours allows the administration of planned doses of chemotherapy on time and significantly reduces the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infection rates [42]. Whilst two studies provided Level II and III evidence that dose intensification is feasible with prophylactic G-CSF [43,44], it is important to note that one study provided important conflicting Level III evidence [46]. Sternberg and colleagues [43] provided Level II evidence that the response rate and OS is not improved following G-CSF-supported dose-intensification, but Level II evidence for an improved PFS (9.1 versus 8.2 months, $P = 0.037$). Similarly, Loehrer and colleagues provided Level III evidence that dose intensification does not improve OS.

No evidence was found for the use of GM-CSF in elderly patients with urothelial tumours.

4. Discussion

A recent meta-analysis of eight randomised, controlled trials, not restricted to an elderly population, has confirmed the value of G-CSF in reducing the risk of febrile neutropenia, documented infection and the need for dose-intensity reduction across disease states and treatment regimens [45]. Comorbid illness may complicate chemotherapy in the elderly and a history of extensive prior cytostatic therapy may have an impact on bone marrow reserves.

The results of our literature research highlight a lack of well-designed clinical trials to assess the use of haematopoietic growth factors in elderly patients with cancer. Very few trials specifically recruited patients aged >70 years and much of the relevant data retrieved originated from studies that did not specifically focus on the elderly, but had a median population age $\geqslant 60$ years. Most of the included data-set reported on the use of G-CSF rather than GM-CSF (24 versus 6 studies).

The data retrieved allowed consideration of the use of prophylactic G-CSF in elderly patients with urothelial cancer, NHL and SCLC, but not breast, colorectal, NSCLC or ovarian cancer. Similarly, evidence on which to base recommendation for the use of GM-CSF was limited to elderly patients with SCLC.

The available evidence endorses the use of prophylactic G-CSF 5 mcg/kg/day to support the administration of planned doses of chemotherapy on schedule in standard chemotherapy settings and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy for NHL, SCLC or urothelial tumours. Lack of available trial data does not allow similar conclusions to be drawn for the other malignancies, but it is likely that similar benefits would accrue from the use of prophylactic G-CSF. There is, however, no evidence that the delivery of standard-dose chemotherapy on schedule improves outcome measures. There is evidence that dose-intensification, mainly achieved through dose interval reduction facilitated by primary prophylactic G-CSF can improve outcome in elderly patients with urothelial cancer, SCLC and NHL (Table 4). Due to the lack of appropriate studies, there is no similar evidence in elderly patients with breast, colorectal, NSCLC and ovarian cancer. However, lack of data should not preclude the use of prophylactic G-CSF for such purposes in elderly patients receiving myelotoxic chemotherapy, but encourage the conduct of the corresponding studies.

It is not possible to make a recommendation for the use of GM-CSF in the elderly (Table 5). The only available data suggests that prophylactic GM-CSF does not reduce the incidence of febrile neutropenia or reduce infections in elderly patients with cancer.

Improved tolerance to chemotherapy may be of particular importance in the elderly population. In a retrospective study of NHL patients receiving CHOP chemotherapy, 140 out of a total of 224 (63%) febrile neutropenic events occurred in patients aged $\geqslant 65$ years and 62% of first febrile neutropenic events occurred within the first two cycles of chemotherapy [6]. In such treatment with a curative intent, evidence of a high probability of reduced tolerance is supportive of the use of primary prophylactic G-CSF in the elderly cancer patient. However, our research provided no data to support the use of prophylactic G- or GM-CSF to reduce the incidence of toxic death. Indeed, in the one disease state in which there was data available (SCLC), prophylactic G- or GM-CSF did not reduce toxic

Table 5
Level of evidence summary table (GM-CSF)

Question	Breast	Colorectal	NHL	NSCLC	Ovarian	SCLC	Urothelial
Toxicity and efficacy during standard-dose chemotherapy							
a	D	D	D	D	D	C	D
b	D	D	B	B	D	C	D
c	D	D	D	D	D	A−ve	D
d	D	D	D	D	D	A−ve	D
e	D	D	D	D	D	A−ve	D
f	D	D	D	D	D	A−ve	D
g	D	D	D	D	D	D	D
h	D	D	D	D	D	A−ve	D
Feasibility and efficacy of dose-intensified chemotherapy							
i	D	D	D	D	D	A−ve	D
j	D	D	D	D	D	D	D
k	D	D	D	D	D	D	D
l	D	D	D	D	D	D	D

GM-CSF, granulocyte macrophage-colony stimulating factor; −ve indicates that the evidence shows a negative recommendation; 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

deaths and in one study, GM-CSF was shown to increase the number of toxic deaths [38]. However, it is important to point out that the reported incidence of toxic deaths in the studies identified was very low and, consequently, a potential impact of CSF would be hard to demonstrate.

There is no evidence that prophylactic G-CSF or GM-CSF improves efficacy outcome measures including response rate, PFS or OS in standard-dose chemotherapy. From the few data available (in NHL and SCLC), it appears that prophylaxis with G-CSF or GM-CSF does not improve outcomes.

Dose-intensification is feasible with the prophylactic administration of G-CSF in elderly patients with NHL, ovarian cancer and SCLC. However, the individual chemotherapy regimen should be carefully considered. G-CSF-supported dose-intensification improves outcomes in patients with NHL [20] and there is supportive evidence of improved survival in patients with SCLC [35,37]. Evidence for the use of G-CSF-supported dose-intensification is lacking in the other disease areas. There is no evidence that GM-CSF-supported dose-intensification has any impact on outcomes in any of the malignancies studied.

In addition to the greater availability of supportive evidence for the use of G-CSF when compared with GM-CSF, an increased incidence of thrombocytopenia following GM-CSF may also restrict the use of the latter administration in elderly patients. Gómez and colleagues [2] noted a significantly increased risk of platelets $<20\times10^9$/l in elderly patients (aged $\geqslant 70$ years) with NHL receiving GM-CSF prophylaxis when compared with those aged from 61 to 69 years ($P=0.0001$).

Advances in cytokine design may have significant benefits, particularly for the elderly population. For example, the addition of a polyethylene glycol molecule to filgrastim results in a novel cytokine, pegfilgrastim, a molecule with a prolonged duration of action that allows once-per-chemotherapy-cycle administration. This offer of a potential positive impact on growth factor compliance combined with a tendency to lower the incidence of febrile neutropenia compared with elderly patients receiving conventional prophylactic G-CSF [16], suggests a possible advantage for pegfilgrastim in this population.

To summarise, the Working Party recommends the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy. There is insufficient evidence to extend this recommendation to include the use of GM-CSF. There are insufficient data available to allow the evaluation of the impact of prophylactic G-CSF on the incidence of toxic death in elderly patients with cancer and this is a crucial question for geriatric oncology practice. There is no evidence that the delivery of standard-dose chemotherapy on schedule improves efficacy measures. However, since febrile neutropenic events are more likely to occur during the first and second cycles of chemotherapy, prophylactic measures should be considered early in the course of treatment. Furthermore, since systematic dose reduction can impact on outcome, we propose either primary prophylactic use of G-CSF for all elderly patients receiving curative myelotoxic chemotherapy (CHOP or CHOP-like) and a risk-adapted strategy with primary prophylactic G-CSF administration in high-risk patients, as suggested by the ASCO guidelines for all patients. Dose intensification facilitated by prophylactic G-CSF has been shown in a small number of trials to provide for improved survival in elderly patients with specific

malignancies (NHL, SCLC), but cannot be recommended without further evidence. Consideration should be shown to the toxicity profile of alternative chemotherapy regimens when deciding on treatment regimens, particularly in the palliative setting. In several specific malignancies, there is a clear need for further well-designed studies and clinically applicable tools to assist the identification of elderly patients who will benefit most from prophylactic G-CSF. To achieve this, the panel strongly urges the design of and participation in further trials.

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