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Delivering optimal adjuvant chemotherapy in primary breast cancer: the role of rHuG-CSF

R. Paridaens[a,*], G.H. Lyman[b], R. Leonard[c], J. Crawford[d], A. Bosly[e], M. Constenla[f], C. Jackisch[g], R. Pettengell[h], T. Szucs[i] on behalf of the Impact of Neutropenia in Chemotherapy European Study Group

[a]*Department of Oncology, University Hospital Gasthuisberg, UZ K.U. Leuven, Herestraat 49, B-3000 Leuven, Belgium*
[b]*James P. Wilmot Cancer Center, University of Rochester, Rochester, New York, USA*
[c]*South West Wales Cancer Institute, Singleton Hospital, Swansea, UK*
[d]*Duke University Medical Center, Durham, North Carolina, USA*
[e]*Cliniques Universitaires UCL, Godinne, Belgium*
[f]*Complexo Hospitalario de Pontevedra, Pontevedra, Spain*
[g]*University of Marburg, Marburg, Germany*
[h]*St George's Hospital, London, UK*
[i]*European Data Collection & Evaluation Center, Basel, Switzerland*

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Abstract

Most patients with operable breast cancer now receive postoperative medical treatment in the form of adjuvant chemotherapy, hormone manipulation or both. These additional interventions have led to a significant improvement in disease-free survival and overall survival. Clinical trials suggest that total chemotherapy dose delivered and dose intensity both affect long-term clinical outcomes, yet clinical practice audits conducted in Europe and the USA show that dose reductions and delays are widely applied when haematological toxicities such as neutropenia occur. In order to reduce the risk of neutropenic complications and help deliver chemotherapy planned dose on time, targeted use of recombinant human granulocyte colony-stimulating factor (rHuG-CSF) in breast cancer patients is recommended. The availability of neutropenia risk prediction models and the first once-per-cycle, fixed-dose rHuG-CSF (pegfilgrastim), will allow more patients to benefit from receiving their planned chemotherapy dose on time, and enable the use of new dose-dense chemotherapy strategies in the adjuvant treatment of primary breast cancer. These hold the prospect of further improving chemotherapy treatment outcomes.

Keywords: Breast cancer; Adjuvant chemotherapy; Neutropenia; Filgrastim; Pegfilgrastim; rHuG-CSF

1. Introduction

Breast cancer remains the most common cancer in women and is the most frequent cause of cancer death [1]. In 1990, an estimated 178,904 new cases of breast cancer were reported in the European Union—representing 28% of all female cancers [1].

Over the past 20 years, the 5-year survival for patients with breast cancer has increased by around 10%, largely as a result of earlier diagnosis and better treatment [2]. Nevertheless, 5-year survival rates for people with breast cancer range between 60% and 70%, and many patients still die from their disease [2].

Early detection and definitive surgical management are the foundation of curative strategies in women with breast cancer [3]. In addition, most patients with operable breast cancer now receive postoperative medical treatment in the form of adjuvant chemotherapy, hormone manipulation or both [4], and these additional interventions have led to a significant improvement in disease-free and overall survival [5,6] (Fig. 1).

Despite these improvements, however, the drive to further enhance breast cancer treatment outcomes

* Corresponding author. Tel.: +32-16-34-69-00; fax: +32-16-34-69-01.
E-mail address: robert.paridaens@uz.kuleuven.ac.be (R. Paridaens).

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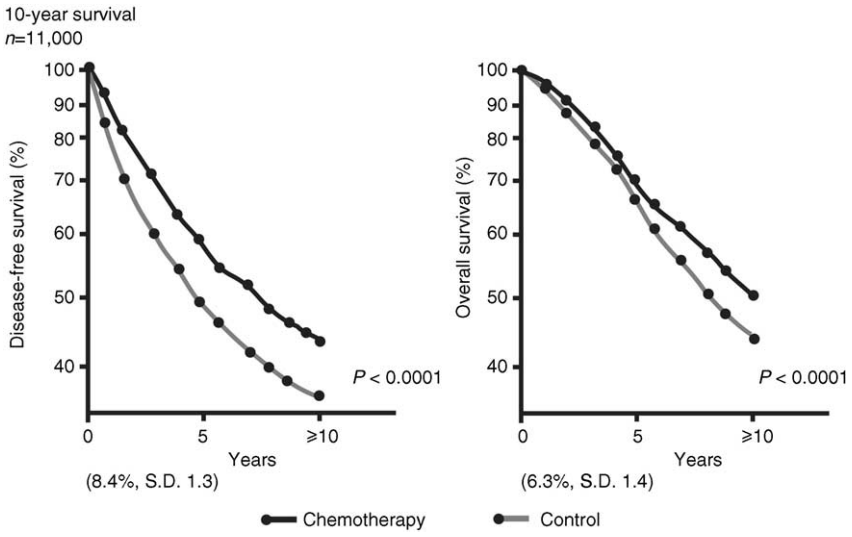

Fig. 1. Ten-year survival benefits of adjuvant chemotherapy in early-stage breast cancer: a meta-analysis of 31 randomised, controlled clinical trials of long-term combination chemotherapy versus no chemotherapy in 11 000 women (adapted from [5]).

continues, and has led to the investigation of putative non-cross resistant combinations of chemotherapeutic agents, the use of different sequences of drug delivery, dose escalation, and the initiation of studies assessing increased dose density.

One of the most important outcomes from recent investigations is the finding that both chemotherapy total dose and dose intensity may impact on long-term clinical outcomes in the adjuvant treatment of primary breast cancer [7–9]. It is therefore of grave concern that there is growing evidence that chemotherapy dose reductions and dose delays are commonplace in clinical practice in Europe and in the USA [10–13].

Treatment-limiting adverse events such as neutropenia appear to be a primary reason for reductions in chemotherapy dose intensity [3] yet neutropenic complications can be greatly reduced through the prophylactic use of recombinant granulocyte colony-stimulating factors (rHuG-CSFs).

In order to optimise outcomes in the adjuvant treatment of primary breast cancer, a number of key issues must therefore be addressed. First, it is important to understand what factors in clinical practice are contributing to the apparent sub-optimal dosing of current chemotherapy combinations, and which patients are at greatest risk of a dose reduction or dose delay. Second, strategies to prevent any reduction in target dose intensity must be developed in order to improve clinical outcomes [7,14–16]. Finally, appropriate use of supportive therapy with agents such as rHuG-CSF must be encouraged in order to help maintain chemotherapy dose intensity [17–19]—especially in the adjuvant treatment of breast cancer [20,21]—but supportive therapy must be targeted selectively at those at greatest risk of dose reductions and dose delays [7], and simplified wherever possible to encourage compliance.

In this supplement, the latest evidence supporting the importance of dose intensity in the adjuvant treatment of primary breast cancer is reviewed, and current trends in the use of breast cancer chemotherapy in community practices are examined. New data on the incidence and risks associated with chemotherapy dose-limiting toxicities such as neutropenia are outlined, and novel approaches to reducing the risk of neutropenia are described.

With a clearer understanding of who is at most risk of dose-limiting chemotherapy toxicity, and armed with more potent and convenient ways to prevent these toxicities, the clinical oncologist will be poised to enter a new era in the adjunctive treatment of primary breast cancer.

2. Dose intensity and outcomes: the latest evidence

Frei and Canellos (1980) demonstrated that a logarithmic increase in cytotoxicity could be achieved with a linear increase in chemotherapy dosage [22]. Frei and Canellos' experimental theory was subsequently confirmed in the clinic, with Hryniuk and other investigators demonstrating retrospectively that an increased dose intensity within the conventional range of cytotoxic drug dosage may have a marked effect on outcomes in breast cancer [23,24].

2.1. Dose intensity in adjuvant breast cancer chemotherapy

Randomised controlled trials and clinical practice audits have confirmed that both total dose and dose intensity of adjuvant chemotherapy may be important variables in disease-free survival and overall survival for

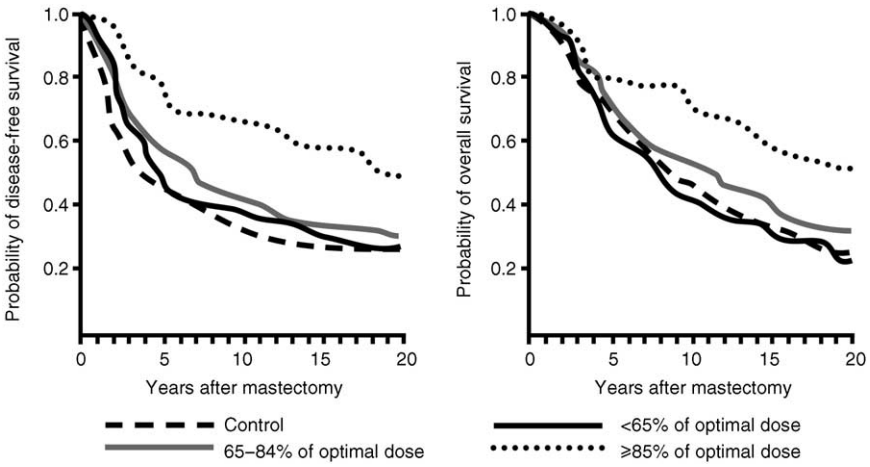

Fig. 2. Relapse-free survival and overall survival according to percentage of optimal chemotherapy dose administered [14]. Copyright © 2003 Massachusetts Medical Society.

patients with operable breast cancer [8,14,15,25]. In one landmark Italian study, 386 women with node-positive breast cancer were randomised to receive either no further treatment after radical mastectomy or 12 monthly cycles of adjuvant combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) [14]. After 20 years of follow-up, both relapse-free and overall survival rates were significantly better in patients treated with surgery plus adjuvant chemotherapy than in patients treated with surgery alone.

A retrospective analysis of this study demonstrated that patients who received at least 85% of their planned optimal chemotherapy dose had substantially better long-term outcomes than patients who did not [14] (Fig. 2). Importantly, recurrence-free survival rates for the women who received less than 65% of their planned chemotherapy dose did not differ significantly from the untreated controls.

The Cancer and Leukemia Group B (CALGB) study 8541 examined the effects of adjuvant treatment in 1550 patients with operable stage II breast cancer using one of three chemotherapy dose levels: a full-dose arm (cyclophosphamide 600 mg/m^2/doxorubicin 60 mg/m^2/fluorouracil 600 mg/m^2), a moderate-dose arm (cyclophosphamide 400 mg/m^2/doxorubicin 40 mg/m^2/fluorouracil 400 mg/m^2), and a low-dose arm (cyclophosphamide 300 mg/m^2/doxorubicin 30 mg/m^2/fluorouracil 300 mg/m^2) [8,15]. Patients in the full-dose arm received twice the dose intensity and twice the total dose as those in the low-dose arm. At a median follow-up of 9 years, disease-free survival and overall survival in the high- and moderate-dose arms were superior to the corresponding survival measures for patients in the low-dose arms [15]. At 5 years, overall survival was 79±2% for patients in the full-dose arm, 77±2% for patients in the moderate-dose arm, and 72±2% for patients in the low-dose arm. Disease-free survival was 66±2%, 61±2%, and 56±2%, respectively [15]. The results of this trial have been interpreted as showing evidence of benefit from achieving a threshold dose intensity, but no additional gain from continuing dose escalation.

Five-year overall survival rates in the French Adjuvant Study Group (FASG) trial [25], which evaluated over 500 patients with poor-prognosis, node-positive operable breast cancer receiving either FEC 50 (fluorouracil 500 mg/m^2/epirubicin 50 mg/m^2/cyclophosphamide 500 mg/m^2) or FEC 100 (fluorouracil 500 mg/m^2/epirubicin 100 mg/m^2/cyclophosphamide 500 mg/m^2), were significantly higher (65.3% and 77.4%, respectively [$P=0.007$]) in patients who received the regimen containing the higher dose of epirubicin [25].

2.2. Dose-dense chemotherapy strategies: the new treatment paradigm?

Two recent studies have tested the relatively new concept of dose density in the adjuvant treatment of primary breast cancer [9,26]. The concept of dose density is based on the experimental observation that a given chemotherapy dose always kills a certain fraction—rather than a certain number—of growing cancer cells [9]. It was therefore hypothesised that more frequent administration of cytotoxic chemotherapy would be a more effective way of minimising the residual tumour burden than dose escalation [9].

In the studies by Hudis *et al.* (1999) [26] and Citron *et al.* (2003) [9], chemotherapy dose density was increased by shortening the interval between chemotherapy cycles from the standard 3-weekly schedule to a more intensive 2-weekly schedule. In the pilot study [26], four cycles of doxorubicin 75 mg/m^2 given every 21 days followed by high-dose cyclophosphamide (3000 mg/m^2) given every 14 days with filgrastim support were evaluated. The study demonstrated the safety and feasibility of using a sequential dose-dense plan, and it paved the way for the first prospective, randomised study comparing both

sequential *versus* concurrent combination chemotherapy and standard *versus* dose-dense regimens [9].

This study has recently been reported by Citron *et al.* on behalf of the CALGB 9741 study investigators [9]. It presents compelling evidence for the benefits of dose-dense chemotherapy strategies in early-stage breast cancer and provides further verification of the importance of chemotherapy planned dose on time. In this study involving over 2000 women with node-positive breast cancer, 2-weekly administration of doxorubicin 60 mg/m^2/paclitaxel 175 mg/m^2/cyclophosphamide 600 mg/m^2 (with a protocol requirement for supportive use of filgrastim) reduced the risk of disease recurrence and death at 3 years by 26% ($P=0.010$) and 31% ($P=0.014$), respectively, compared with a conventional 3-weekly dosing schedule [9]. No differences were found in either disease-free survival or overall survival between concurrent or sequential chemotherapy scheduling.

3. Consequences of chemotherapy-induced neutropenia

Although clinical trial evidence now suggests that sustaining or even increasing chemotherapy dose intensity may optimise the outcomes of adjuvant treatment for primary breast cancer, haematological toxicity—especially neutropenia—often necessitates a chemotherapy dose reduction or dose delay in clinical practice [27,28]. Such dose modifications have a significant impact on the relative dose intensity of treatment received, and may potentially compromise survival outcomes.

In addition to dose modifications, neutropenia increases the risk of developing serious microbial infections subsequent to chemotherapy [29] and can lead to febrile episodes that require hospitalisation and intravenous antibiotic treatment [30]. Fatal neutropenic complications occur in approximately 5–7% of febrile neutropenic episodes, which is a catastrophic outcome in otherwise well patients being treated to reduce their risk of cancer recurrence.

3.1. Incidence and duration of neutropenia

Systematic reviews of the literature provide conflicting reports of the rates of grade 3 or 4 neutropenia experienced with commonly employed chemotherapy regimens in primary breast cancer. Dale *et al.* have suggested that up to 78% of women may experience grade 3 or 4 neutropenia or leukopenia with CMF regimens and up to 100% of women may suffer such complications with cyclophosphamide/anthracycline/fluorouracil (CAF) or fluorouracil/epirubicin/cyclophosphamide (FEC) therapy [31].

Retrospective clinical practice audits conducted during the late 1990s in the USA [12], Spain [10], Belgium and Luxembourg [11] and the United Kingdom [13] (Table 1), found that, overall, 30–40% of all breast cancer patients experienced a chemotherapy-induced neutropenic event, and that 5–8% developed febrile neutropenia. In the UK audit, 29% (121/422 patients) of patients treated with adjunctive chemotherapy for stage I–III breast cancer experienced at least one neutropenic event, with CMF-based regimens producing a similar incidence of neutropenia (29% of patients) to anthracycline-based regimens (28% of patients) [13].

A direct relationship has been observed between the duration of severe neutropenia and the incidence of febrile neutropenia [32]. In a recently reported study [31], the estimated odds ratio for febrile neutropenia was 2.3 per day increase in the duration of severe neutropenia. Other recent studies have shown that the risk of febrile neutropenia is greatest in the first cycle of chemotherapy treatment [33].

3.2. Chemotherapy dose reductions and delays

Neutropenia represents the most common dose-limiting adverse effect of cytotoxic cancer chemotherapy, with retrospective studies in the USA and Europe suggesting that neutropenic complications in the adjuvant breast cancer chemotherapy setting result in treatment delays in up to 40% of patients, and chemotherapy dose reductions in approximately 25% patients (Fig. 3) [10–13].

As a consequence of these dose delays or reductions, it has been estimated that up to one-third of patients in clinical practice currently receive less than 85% of their planned relative dose intensities [3]. Even minor dose reductions or delays can have a major impact on delivered dose intensity [18], and this could compromise long-term treatment effectiveness and disease control [12,18].

Concurrent radiation therapy may also increase the risk of a dose reduction or dose delay, thus jeopardising

Table 1
European and US clinical practice audits in the management of primary breast cancer: overview of retrospective studies

	UK audit [13]	Chemodose [11]	OSQAR [10]	INC study	ChemoInsight [12]
Country of audit	UK	Belgium and Luxembourg	Spain	USA	USA
Stage I–III patients (*n*)	422	592	1078	2092	20 799
Centres	15	37	34	87	1243
Time period	1997–1999	1996–1999	1993–2001	1993–2001	1997–2000

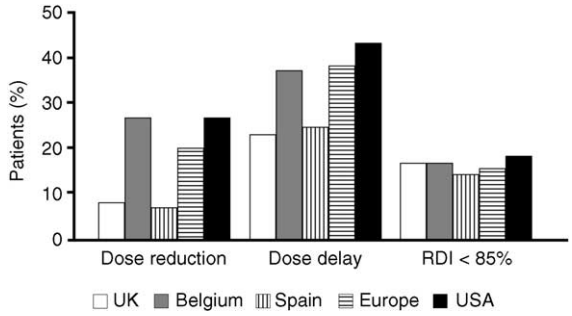

Fig. 3. Incidence of dose reductions and dose delays in clinical practice audits in the UK [13], Belgium and Luxembourg [11], Spain [10] and the USA [12].

the delivery of the intended relative total dose intensity [34,35].

3.3. Risks associated with febrile neutropenia

Although chemotherapy-induced neutropenia can generally be managed well with hospital admission and careful observation, the cost and consequences can be considerable [28]. Community-based surveys suggest that around 7% of cancer patients admitted to hospital with neutropenia may die while in hospital, with risk of death increasing with age, the presence of comorbidities, and the length of hospital stay [36].

Mortality associated with Gram-negative sepsis in neutropenic patients is estimated to be between 10% and 30%, despite the prophylactic use of increasingly potent broad-spectrum antibiotics [29].

The standard treatment for documented febrile neutropenia includes hospitalisation and immediate empirical therapy with broad-spectrum intravenous antibiotics. Hospitalisation for febrile neutropenia typically lasts 4–7 days, although prolonged hospitalisation for several weeks may be required [37,38]. Studies in the USA suggest that approximately one-third of patients with febrile neutropenia are hospitalised for 10 days or more, and nearly 80% of the healthcare costs associated with febrile neutropenia can be attributed to these long-stay patients [37].

4. Improving outcomes with growth factor support in early-stage breast cancer

Since achieving or even increasing the target chemotherapy dose intensity clearly improves the outcome of adjunctive therapy in early-stage breast cancer, predicting which patients are at risk of dose-limiting myelotoxicity, and reducing that risk pre-emptively, appears to be the most logical management approach [7]. Recombinant granulocyte colony-stimulating factor (rHuG-CSF) has been shown consistently to reduce the

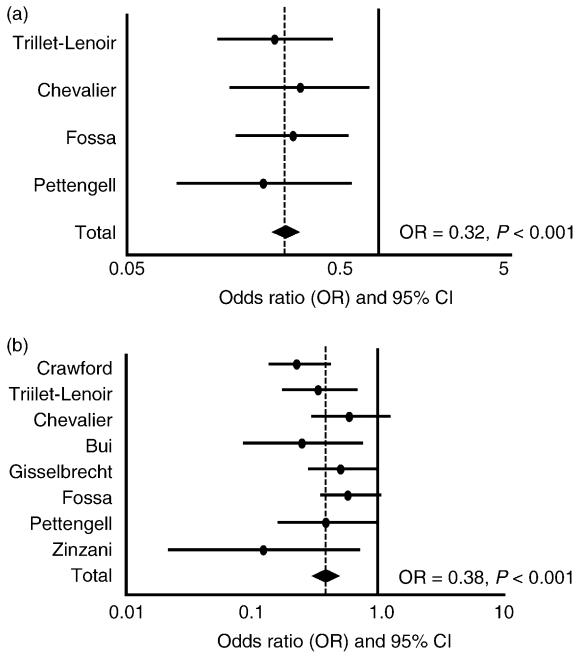

Fig. 4. Forest plot of the odds ratio (on a logarithmic scale) for febrile neutropenia (a) and chemotherapy dose reduction (b) in controlled clinical trials assessing the prophylactic efficacy of rHuG-CSF when used following systemic chemotherapy [47]. Reprinted from [47], with permission from Excerpta Medica, Inc.

severity and duration of neutropenia in patients being treated with systemic cancer chemotherapy [39–41], and to reduce the risk of febrile neutropenia in patients receiving dose-intense regimens [17–19,42–46].

A recent meta-analysis of eight randomised controlled studies has confirmed that prophylactic use of rHuG-CSF in patients receiving cancer chemotherapy was associated with a reduced risk of febrile neutropenia (odds ratio [OR] = 0.38), documented infection (OR = 0.51) and infection-related mortality (OR = 0.60), and significantly reduced the risk of a chemotherapy dose reduction or dose delay ($P = 0.001$) [47] (Fig. 4). In patients who did not receive rHuG-CSF support, 34% required a chemotherapy dose reduction, compared with 15% of patients who received rHuG-CSF [47].

Use of rHuG-CSF support in the adjuvant treatment of breast cancer has also been shown to enable the use of full doses of chemotherapy in node-positive [21] and metastatic breast cancer [48], and to be cost-effective when used for this purpose [49]. Most recently, administration of filgrastim enabled the administration of dose-dense (i.e. 2-weekly) combination adjuvant chemotherapy for primary breast cancer, with significant survival benefits being reported over 3-weekly scheduling [9].

Although these studies provide unequivocal evidence for the benefits of rHuG-CSF support in preventing neutropenic complications and associated chemotherapy dose reductions or delays, prospective rando-

mised studies are required in order to confirm that these benefits have a positive impact on survival outcomes.

4.1. Developing neutropenia risk models

Despite the published evidence supporting the benefits of rHuG-CSF in the adjuvant cancer chemotherapy setting, clinical practice audits reveal that fewer than 15% of patients receiving chemotherapy for breast cancer across Europe receive rHuG-CSF support [10,11,13] (Fig. 5). By comparison, in the USA, nearly 30% of patients receiving adjuvant breast cancer chemotherapy are treated with rHuG-CSF [12] (Fig. 5).

Although it is difficult to establish precisely what factors are preventing the effective use of rHuG-CSF support in the breast cancer treatment setting, it is broadly agreed that the ability to predict which patients may become neutropenic or require a dose delay or reduction would allow more targeted and therefore more cost-effective employment of these agents [7,28,50].

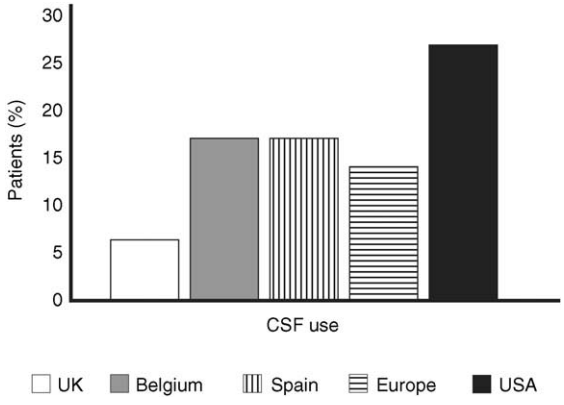

Fig. 5. Use of CSF in Europe: summary of findings from clinical practice audits in the UK [13], Belgium and Luxembourg [11], Spain [10] and the USA [12].

Several clinical prediction models for chemotherapy-induced neutropenia have been proposed in the past [28,50,51] and all have merit, despite the limitations inherent in using retrospective data to build prediction hypotheses [52] (Fig. 6). Silber *et al.* (1998) studied 95 patients who had received standard-dose adjunctive chemotherapy for early-stage, non-metastatic breast cancer, and found that the depth of the first-cycle absolute neutrophil count (ANC) nadir and the decline in haemoglobin levels were reliable predictors of neutropenic events in subsequent cycles, and that chemotherapy plus radiotherapy also increased the risk of subsequent events [28]. Similarly, Dumez *et al.* (1999) analysed predictors of dose and dose intensity in 99 patients with stage II node-positive breast cancer who received post-operative adjuvant chemotherapy with the 'classical' CMF regimen. They found that patients receiving concomitant radiotherapy, and/or having low white blood cell counts at day 8 of their first cycle were at high risk of receiving sub-optimal total doses and a low dose intensity [53].

The importance of the first-cycle ANC nadir as a predictor of subsequent neutropenic complications has also been confirmed by Thomas *et al.* (2001) [54], who demonstrated that patients with a first-cycle ANC nadir $<500/\mu l$ experienced a significantly greater number of episodes of febrile neutropenia (16% versus 0%; $P=0.04$), and were significantly more likely to receive $<85\%$ of their planned dose intensity (39% versus 14%; $P=0.02$).

Predictive neutropenia risk models based on large-scale prospective studies are currently in development, and a preliminary analysis of data from the ongoing *Awareness of Neutropenia in Chemotherapy* (ANC) Registry in the USA, has confirmed the feasibility of

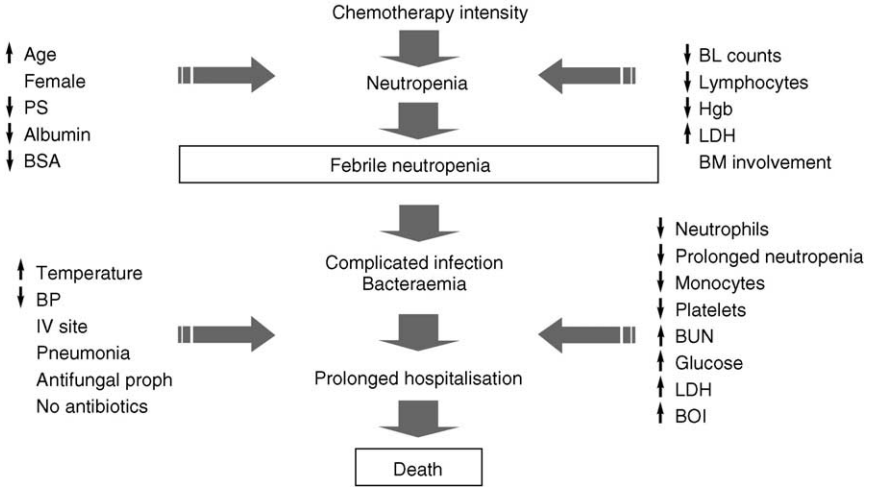

Fig. 6. Schematic illustration of the course of neutropenia and its complications resulting from the myelosuppressive effects of cancer chemotherapy [49]. Reprinted from [49], with permission from Lippincott Williams & Wilkins.

this approach to risk modelling [52]. The ANC Study, which currently includes approximately 100 community oncology practices, and over 200 patients who have received chemotherapy for breast cancer, found that 41% of patients had first-cycle ANC nadirs of less than 1×10^9/L and 26% of patients had first-cycle nadirs of less than 0.5×10^9/L [52]. Patients were more likely to experience neutropenia if they had early-stage disease (stages I–III), were older (>65 years), or if they had received an anthracycline-containing chemotherapy regimen [52]. In addition, more patients were treated with antibiotics and supportive growth factors in chemotherapy cycle 2 than in cycle 1 [52].

Although these data are only provisional, it is hoped that a longer period of follow-up and further analysis of results from this study will be used to develop and validate an effective risk model to help identify patients at greatest risk of neutropenic complications. Once available, such a tool would provide a valuable aid to clinical decision making and avoid compromised chemotherapy by targeting appropriate supportive measures to patients at risk [52]. Such an approach has been used successfully by Moore *et al.* (2001) [55] and Rivera *et al.* (2001) [56], who stratified patients according to their first-cycle ANC nadir (patients with ANC nadir <500/μl were considered high risk) and targeted rHuG-CSF support in subsequent chemotherapy cycles at those considered high risk. The majority of patients given targeted therapy in this way ultimately received their planned chemotherapy dose on time [55,56], and the risk of febrile neutropenia and febrile neutropenia-related hospitalisation were significantly reduced [56].

The concept of pre-emptive use of rHuG-CSF has also been tested prospectively by Paridaens *et al.* (2002) [57], who conducted a randomised clinical trial in 102 patients with operable breast cancer receiving adjuvant CMF with concomitant radiotherapy after their surgery. At the first event affecting chemotherapy dose intensity, patients were randomised to continue with their chemotherapy with filgrastim support (Group A) or to continue without filgrastim (Group B) in subsequent cycles. Of the 37 randomised patients, 53% of those in Group A but only 17% of those in Group B could maintain a dose intensity above 90% [57].

Pre-emptive strategies such as this are clearly safer than secondary prophylaxis, when rHuG-CSF is initiated only after the occurrence of a life-threatening event such as febrile neutropenia. They are also significantly more cost-effective than indiscriminate primary prophylaxis, in which all patients receive rHuG-CSF. However, despite the potential benefits of pre-emptive use of rHuG-CSF in breast cancer chemotherapy, optimal 1st-cycle neutropenia risk models have yet to be defined, and such strategies need to be further evaluated in prospective, randomised studies in order to confirm that they translate into long-term survival benefits.

4.2. Developing novel haematopoietic growth factors

Many studies have examined recombinant human granulocyte colony-stimulating factor (rHuG-CSF, filgrastim) in the management of neutropenia caused by cancer chemotherapy, and these have been reviewed by Welte *et al.* (1996) [41]. Administration of filgrastim has been shown to increase white blood cell counts and decrease the duration of neutropenia, to reduce the number of days of hospitalisation, and reduce the number of culture-confirmed infections [39,58–60].

The serum half-life of filgrastim is approximately 3 h in humans [61], which generally necessitates daily administration by subcutaneous (SC) injection for up to 2 weeks following each myelosuppressive chemotherapy cycle [62]. This requires a high level of compliance in a population of patients that may already be severely debilitated [63].

The quest to possibly improve the quality of life for cancer patients by simplifying treatment has recently led to the use of pegylation technology to improve the pharmacokinetic profiles of several well-established adjuvant treatments [62]. Attaching polyethylene glycol (PEG) to the agent is an increasingly common way to extend the pharmacological activity of parenterally-administered treatments in order to allow a reduction in the duration of treatment or the number of doses of treatment required [62].

Pegfilgrastim (Neulasta®) is a bioengineered form of rHuG-CSF that has been created by attaching a PEG molecule at the N-terminal methionine residue of the filgrastim protein. Pegfilgrastim stimulates the production and maturation of neutrophil precursors and enhances the function of mature neutrophils in the same manner as filgrastim. However, pegylation has extended the duration of action of filgrastim such that a single, fixed-dose of pegfilgrastim can be administered once per chemotherapy cycle [63].

Data from normal volunteer studies [61] and studies in cancer patients [64] have indicated prolonged serum levels of pegfilgrastim, with 'self-regulation' of drug concentrations as a function of neutrophil clearance [63]. Pegfilgrastim has a sustained duration of effect relative to filgrastim because of decreased renal clearance, resulting in clearance almost exclusively by neutrophils. A prolonged terminal half-life and self-regulation in this way allows less frequent dosing and the maintenance of more stable neutrophil levels [63]. Two large, double-blind, randomised clinical trials (Fig. 7), have compared a single fixed dose (6 mg) or a weight-based single dose (100 μg/kg) of pegfilgrastim with a weight-based daily dose (5 μg/kg) of filgrastim in patients with high-risk breast cancer [63,65]. In the first study, 157 patients were randomised to receive either a single 6 mg subcutaneous injection of pegfilgrastim or daily subcutaneous injections of filgrastim (5 μg/kg)

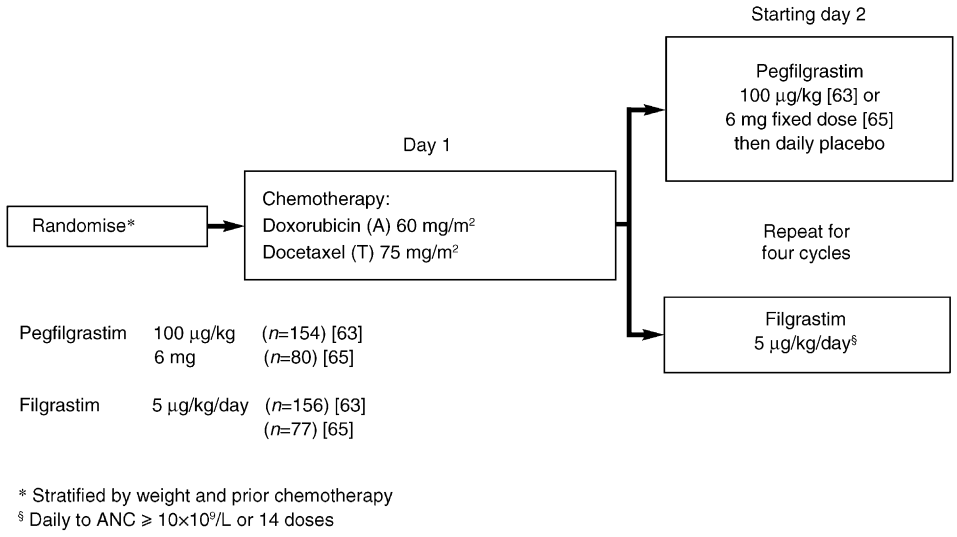

Fig. 7. Design of pivotal, phase III clinical trials of pegfilgrastim in the treatment of women with breast cancer [63,65].

Table 2
Incidence and severity of neutropenia and febrile neutropenia in two double-blind studies of single-dose pegfilgrastim versus daily filgrastim in the treatment of breast cancer [63,65]

	(Green *et al.*, 2003) [65]		(Holmes *et al.*, 2002) [63]	
	Pegfilgrastim fixed 6 mg ($n=77$)	Filgrastim 5 µg/kg/d ($n=75$)	Pegfilgrastim 100 µg/kg ($n=149$)	Filgrastim 5 µg/kg/d ($n=147$)
Incidence of grade 4 neutropenia (%)[a]				
Cycle 1	84	83	77	79
Cycles 2–4	51–57	49–54	37–45	55–60
Mean duration of grade 4 neutropenia (d)[a]				
Cycle 1	1.8	1.6	1.7	1.8
Cycles 2–4	1.0–1.1	0.9–1.0	0.6–0.9[f]	1.1–1.3
Incidence of febrile neutropenia (%)[b]				
All cycles	13	20	9[e]	18
Time to ANC recovery (d)				
All cycles	9[c]	9[c]	9.3[d]	9.7[d]

[a] Absolute neutrophil count (ANC) $<0.5 \times 10^9$/l.
[b] Oral temperature $\geqslant 38.2\,^{\circ}C$ and ANC $<0.5 \times 10^9$/l.
[c] Median.
[d] Mean.
[e] $P=0.029$ (CL −16.8 to −1.1%).
[f] $P \leqslant 0.02$ (CL 0.71, −0.07) versus filgrastim.

after doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 [65]. In the second study, 310 patients were randomised to receive either a single subcutaneous injection of pegfilgrastim 100 µg/kg or daily subcutaneous injections of filgrastim (5 µg/kg) after doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 [63]. The primary end-point in both of these studies was the incidence and duration of severe (grade 4) neutropenia (defined as ANC $<0.5 \times 10^9$/l) during cycle 1 of the chemotherapy.

The results of both of these studies are summarised in Table 2. A single dose of pegfilgrastim was as effective as daily filgrastim in terms of reducing the incidence and duration of severe neutropenia and the depth of the ANC nadir in all chemotherapy cycles [63,65] (Fig. 8).

In the larger of the two studies, the duration of severe neutropenia in cycles 2, 3 and 4 was significantly shorter with pegfilgrastim than with filgrastim and the overall incidence of febrile neutropenia (oral temperature $>38.2\,^{\circ}C$ and ANC $<0.5 \times 10^9$/l) was lower (9% versus 18%; $P=0.029$) [63]. The ANC values through nadir and the rate of ANC recovery were similar with both agents, however, a moderate over-shoot in ANCs was observed in the filgrastim treatment groups compared with the pegfilgrastim treatment groups [65] (Fig. 9).

The single, fixed-dose of pegfilgrastim was shown to be equally effective across a broad range of body weights, including patients weighing up to 132 kg [65].

A combined analysis of these two phase III clinical trials has enabled a more robust comparison to be made between active treatment groups, and a more valid assessment of high-risk sub-groups and other secondary clinical endpoints [66]. In this combined analysis, pegfilgrastim significantly reduced the incidence of febrile neutropenia (FN) compared with filgrastim (11% versus 19%; $P<0.05$), which can be interpreted as a 42% reduction in FN risk with pegfilgrastim versus filgrastim [66]. Compared with no rHuG-CSF treatment, once-per-cycle pegfilgrastim therefore results in a 71% relative reduction in the incidence of FN [66] (Fig. 10).

A trend towards a lower risk of hospitalisation and i.v. antibiotic use was also observed in patients receiving pegfilgrastim compared with those receiving filgrastim [66].

Pegfilgrastim was well tolerated in both pivotal studies, and the adverse event profile was similar to that seen with filgrastim [63,65]. The most frequently reported adverse event in both treatment arms was bone pain (25–37% of patients across treatment groups) [62].

These studies have therefore confirmed that once-per-cycle pegfilgrastim provides neutrophil support in the adjuvant treatment of breast cancer that is at least equivalent to that seen with daily filgrastim, without compromising safety or tolerability [63,65].

Once-per-cycle administration in a single, fixed-dose injection simplifies the management of neutropenia for healthcare professionals, patients and caregivers and should help to ease the burden associated with reducing the risk of chemotherapy-induced neutropenia. Studies

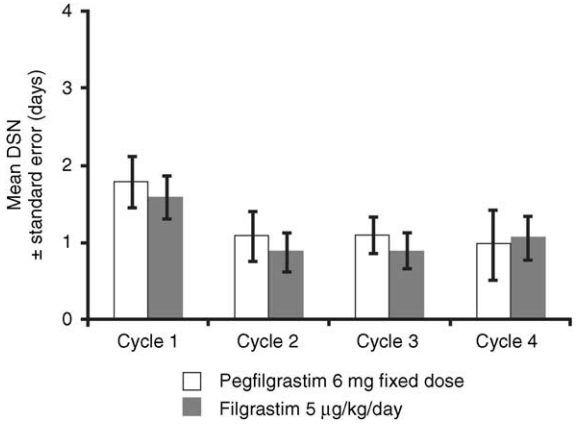

Fig. 8. Duration of severe neutropenia (DSN) in four breast cancer chemotherapy cycles: comparison of efficacy of a single, fixed dose of pegfilgrastim with daily filgrastim (adapted from [65], Table 3).

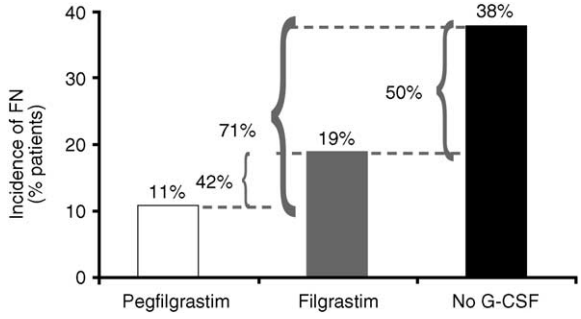

Fig. 10. Relative reduction in the incidence of febrile neutropenia with pegfilgrastim and filgrastim [66] relative to an historic control [67] (adapted from [66]).

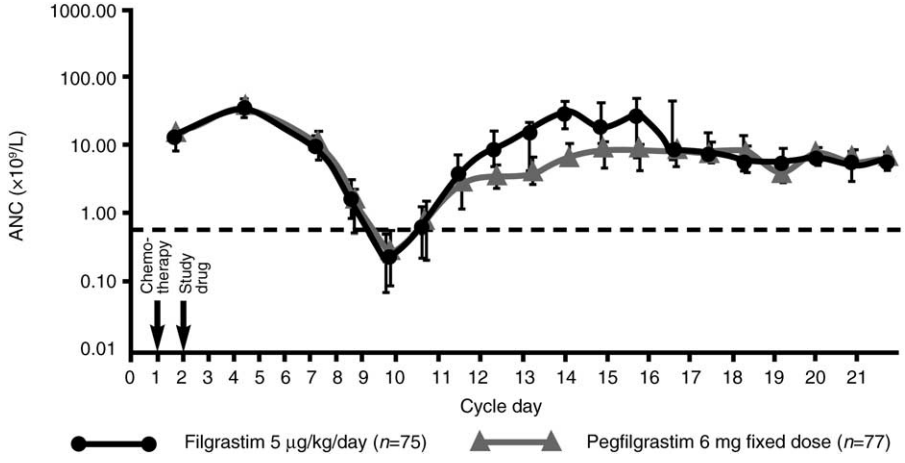

Fig. 9. Median absolute neutrophil count (ANC) for breast cancer chemotherapy cycle 1: comparison of efficacy of a single fixed-dose of pegfilgrastim with daily filgrastim [65]. *Ann Oncol* 2003, **14**, 29–35 by permission of Oxford University Press.

are underway to confirm the safety and feasibility of administering pegfilgrastim concurrently with breast cancer chemotherapy regimens.

5. Conclusions

Maintaining target chemotherapy dose intensity or increasing the dose density are now known to improve clinical outcomes in the adjuvant treatment of primary breast cancer. However, neutropenic complications associated with breast cancer chemotherapy commonly result in chemotherapy dose delays and dose reductions. In routine clinical practice these may result in a significant number of patients being at risk of compromised treatment outcomes.

Use of filgrastim in the adjuvant breast cancer setting reduces the incidence and severity of neutropenic events and has been shown to support an increase in chemotherapy dose intensity. Preliminary studies suggest that this approach may be associated with improved survival.

Pegfilgrastim—a potent, pegylated rHuG-CSF that can be administered once every chemotherapy cycle—builds on the established benefits of filgrastim but with a simplified dosing regimen for improved compliance and possibly enhanced patient quality of life. Pegfilgrastim effectively reduces the duration and incidence of febrile neutropenia in patients receiving adjuvant chemotherapy for primary breast cancer and should help to ensure that more patients receive their planned chemotherapy dose on time.

Validated clinical risk models, built on the basis of data generated in large-scale prospective studies, will help to predict who is at risk of neutropenic complications and reductions in chemotherapy dose intensity, and will allow more targeted prophylactic use of supportive agents such as pegfilgrastim.

Targeted prevention of neutropenic complications associated with adjunctive chemotherapy in breast cancer will allow more patients to receive optimal treatment, and more patients to benefit from dose-dense chemotherapy strategies in the future.

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