The importance of prophylactic management of chemotherapy-induced neutropenia

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The development of colony-stimulating factors (CSFs) has provided clinicians with a valuable tool for proactive management of chemotherapy-induced neutropenia. However, clinicians are also presented with the challenge of appropriately targeting this treatment to patients at serious risk of neutropenic complications, while maintaining an economic approach to prescribing. This article discusses the seriousness of chemotherapy-induced neutropenia and reviews current approaches to the management of this condition. Febrile neutropenia risk models, new therapy options and international guidelines for the use of CSFs are also discussed. ***Anti-Cancer Drugs*** **14:725–730 © 2003 Lippincott Williams & Wilkins.**

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Introduction

In recent years, developments in chemotherapy regimens have improved tumor response and survival in selected patients and disease states. However, some of these newer regimens are associated with increased risks of myelotoxicity and infection. Myelosuppression is the major dose-limiting toxicity of systemic cancer chemotherapy [1], and neutropenia-associated infection is a common cause of morbidity and mortality in patients with cancer. Neutropenia is clinically recognized when the absolute neutrophil count falls below normal levels (1.5–7×10^9/l for a healthy adult). The depth of the absolute neutrophil count nadir defines the severity of neutropenia. Febrile neutropenia (FN) is defined as a body temperature of over 38.2°C accompanied by severe neutropenia (neutrophil count below 0.5×10^9/l) [2].

A relationship was demonstrated between white blood cell (WBC) count and risk of infection in patients with acute leukemia as early as the 1960s [3]. An increased WBC count was linked to a lower infection rate, while increased time with granulocyte and lymphocyte counts below 0.5×10^9/l was linked to more severe infection. The infection-related mortality rate was also higher with decreased granulocyte levels. More recently, data from patients with breast cancer receiving myelosuppressive chemotherapy have shown that the incidence of FN increased significantly as the duration of severe neutropenia (DSN) increased ($p < 0.001$) [4]. With a DSN of 5 days, the probability of a FN event was estimated at 50%. The incidence of culture-confirmed infections was also significantly higher in patients with FN than in those without FN (24 versus 7%; $p < 0.001$) [4].

Frequency of chemotherapy-induced neutropenia

In order to better understand the problems associated with chemotherapy-induced neutropenia, various groups have attempted to quantify the frequency of this condition. The Canadian Database Initiative documented a 42% incidence of at least one neutropenic complication (defined as an FN event, chemotherapy dose reduction of 10% or more or dose delay of 1 week or more) in 444 patients with breast cancer receiving a variety of adjuvant chemotherapy regimens, with 72% developing further complications [5]. Furthermore, the American Society of Clinical Oncology (ASCO) Growth Factors Expert Panel indicated that the incidence of FN with common chemotherapy regimens is up to 40% in chemotherapy-naïve patients [6]. Similarly, the European Society of Medical Oncology (ESMO) suggests that the rate of FN varies from 10 to 57% and grade 4 leukopenia from 2 to 28% for patients receiving standard-dose chemotherapy [7]. Table 1 provides some examples of the type and frequency of myelotoxic and related side-effects associated with different chemotherapy regimens.

Neutropenia incidence is increased during early cycles of chemotherapy

A number of studies have reported when, during the total period of chemotherapy treatment, neutropenia is most frequently observed. In a retrospective, multicenter study of 577 patients with non-Hodgkin's lymphoma (NHL), 56% were admitted to hospital for FN in the first cycle (Fig. 1) [12]. Similarly, first-cycle hematological toxicity was seen in 70% of patients with breast cancer receiving adjuvant chemotherapy, with 68.8% of these

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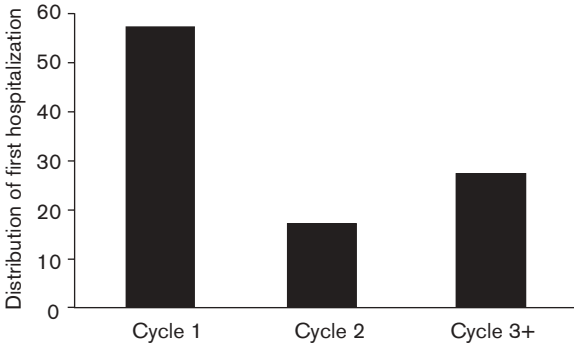
Table 1 The frequency of myelotoxic side-effects associated with some common chemotherapy regimens

Chemotherapy regimen	Patient group	Side-effects of chemotherapy
CHOP or CNOP induction therapy	elderly patients; aggressive NHL	grade 4 granulocytopenia was observed in 91% of patients and infections resulted in hospitalization of 47% of patients with granulocytopenia [8]
High-dose paclitaxel	female patients; metastatic or locally advanced breast cancer	grade 3 or grade 4 granulocytopenia patients, with FN in up to 18% of patients [9]
Docetaxel, cisplatin	advanced non-small cell lung cancer	neutropenia was reported in two-thirds of patients [10]
Cyclophosphamide, doxorubicin, etoposide	small-cell lung cancer	neutrophil count $< 0.5 \times 10^9$/l was observed in 98% of patients [11]

CHOP=vincristine, doxorubicin, prednisone, cyclophosphamide; CNOP=vincristine, mitozantrone, prednisolone, cyclophosphamide.

Fig. 1



Distribution of first hospitalization for FN by chemotherapy cycle in patients with NHL. Adapted from [12].

cases attributable to an absolute neutrophil count below 1×10^9/l [13]. In another retrospective analysis, the risk factors associated with treatment-related death were analyzed in 267 patients with NHL aged between 60 and 94 receiving chemotherapy. Of the 35 chemotherapy-related toxic deaths reported, the majority (63%) occurred during the first cycle of chemotherapy. Infection accounted for 82% of all toxic deaths and two-thirds of the patients that died had an absolute neutrophil count below 0.5×10^9/l [14].

Chemotherapy-induced neutropenia and quality of life (QoL)

Until recently, there has been a scarcity of data reporting the impact of chemotherapy-induced neutropenia on patients' QoL. However, this relationship has now been evaluated by measuring QoL and absolute neutrophil count throughout the first cycle of chemotherapy in 62 patients with various types of cancer [15]. Large declines in absolute neutrophil count were correlated with worse QoL scores for social functioning, distress, despair and general physical symptom scales. Furthermore, patients with grade 4 neutropenia in cycle 1 had significantly greater QoL decreases—measured using domestic environment, social environment and total 'psychosocial adjustment to illness' scales ($p < 0.05$ in all cases)—than patients with grade 0–3 neutropenia. The authors concluded that chemotherapy-induced neutropenia is associated with QoL impairments that can persist even after recovery from neutropenia. None of the patients received prophylactic growth factors and the authors suggested that the role of prophylactic growth factors in preventing QoL impairments warrants further exploration.

To facilitate the measurement of QoL, the Awareness of Neutropenia in Chemotherapy Group has developed a neutropenia-specific QoL instrument, FACT-N (Functional Assessment of Cancer Therapy-Neutropenia) [16]. In the FACT-N validation study, a significant reduction in QoL was shown from day 1 to day 12 of the chemotherapy cycle (60.71 versus 52.45; $p < 0.01$), indicating that patients' QoL worsens around the time of the neutrophil nadir [16].

Chemotherapy dose reduction and neutropenia

In addition to decreased patient QoL, the impact of neutropenia on a patient's anticancer treatment must be considered. The effect of neutropenia on the timely administration of the planned dose of chemotherapy has been widely documented, with neutropenia being the major dose-limiting toxicity of chemotherapy [5].

Chemotherapy dose reductions have been linked to significantly lower complete response rates and shortened survival in a number of cancers. In breast cancer patients receiving chemotherapy, 5-year relapse-free survival was 77 versus 48% for patients receiving 85% or higher versus below 65% of the planned dose, respectively [17]. A 20-year follow-up study confirmed the survival benefits of maintaining planned doses [18]. Similarly, NHL patients had a decreased response rate (65 versus 79%; $p = 0.01$) and lower 2-year survival rate (61 versus 72%; $p = 0.02$) when patients receiving 70% or less relative dose intensity (RDI) were compared with those receiving more than 70% RDI [19].

Approximately three-quarters of patients with NHL have neutropenia-associated treatment delays of 7 days or greater [20]. The UK Audit of primary breast cancer patients revealed that the occurrence of neutropenic

events had a significant impact on the chance of patients achieving planned chemotherapy dose on time [21]. Out of a total of 422 patients evaluated in this audit, 29% of patients experienced at least one neutropenic event and 11% of patients received less than 85% of the planned dose intensity. Mean RDI was significantly lower in patients who had a neutropenic event than in those who did not ($p < 0.01$) and almost 40% of these patients who experienced a neutropenic event had below 85% of the planned dose intensity compared with only 9% of patients who were free of neutropenic events.

Neutropenia-related infection and anti-infective therapy

Before specifically discussing the various options available to manage neutropenia, it is useful to consider the neutropenic patient's ability to fight infection. Low neutrophil counts compromise the immune system, making patients vulnerable to infection and increasing the need for hospital admission. A low absolute neutrophil counts also compromises the inflammatory response so it may be difficult to detect early signs of infection leading to the development of advanced disease. As a result, unplanned hospital admission, together with the administration of i.v. antibiotics and antifungals, is often necessary. Furthermore, the proportion of time spent with low granulocyte levels (below 0.5×10^9/l) was seen to increase with more severe infection [3]. The mortality rate in cancer patients with FN is approximately 10%, with 2% due to an initial infection during an episode of FN. Further infection and progressive cancer explain the overall 10% mortality in patients with FN [22].

Although the response rate with appropriately administered, empirical antimicrobial therapy is currently still high [23], the potential limitations should not be forgotten. Administration of antibiotics usually leads to colonization of bodily surfaces with antibiotic-resistant rather than antibiotic-sensitive organisms and the ongoing problems associated with resistant strains must be seriously considered at all times. Furthermore, fungal infection is a well-recognized complication of continued antibiotic therapy, particularly in neutropenic patients [24]. Long-term neutropenia also reduces response rates to anti-infectives by as much as 30% [25]. The prophylactic use of antibiotics to minimize chemotherapy-related infection, therefore, has been questioned [23], especially as alternative strategies are available to prevent the development of neutropenia in patients receiving chemotherapy. Such strategies include the use of recombinant colony-stimulating factors (CSFs).

Management of neutropenia using CSFs

The proactive management of neutropenia with CSFs can be divided into two main categories. Primary prophylaxis is the planned use of CSFs in the first cycle and in all subsequent cycles of chemotherapy. Conversely, secondary prophylaxis is the planned use of CSFs following an episode of severe neutropenia and then in all subsequent cycles of chemotherapy.

Prophylactic, repeated, daily doses of granulocyte CSF (G-CSF) reduce the duration of chemotherapy-induced neutropenia in patients with several tumor types [11]. In addition, CSFs reduce treatment delays [26] and improve the administration of planned chemotherapy dose on schedule [26,27]. However, if primary prophylactic G-CSF was given to all cancer patients receiving chemotherapy, approximately 60% may have been treated unnecessarily as they would have been unlikely to develop FN on standard chemotherapy regimens [6].

Updated risk threshold analyses and risk models

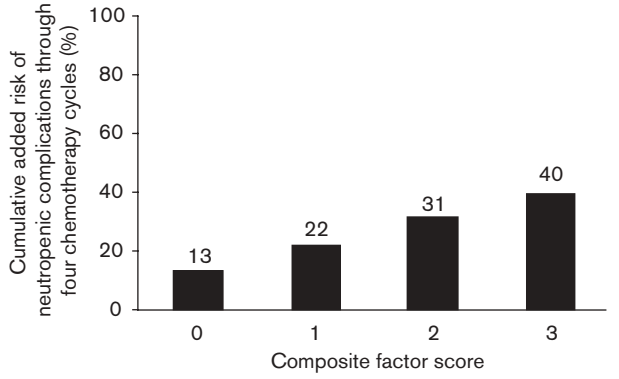
In order to identify patients at risk of developing FN, clinical prediction models are required to identify those patients most in need of prophylactic G-CSF for neutropenia. Such models should also lead to increased cost-efficiency and improved allocation of resources.

Various, specific risk factors for developing FN have been identified. The Awareness of Neutropenia in Chemotherapy Group has reported that rates of hematological toxicity, including FN, are higher with increasing age (65 years or older), low baseline absolute neutrophil count, low body surface area, white race and with certain chemotherapy regimens [13,28–30].

The Silber prediction tool [31] is a validated model developed in patients with breast cancer receiving standard-dose adjuvant chemotherapy. Logistic regression revealed that the depth of the first-cycle absolute neutrophil count was an excellent predictor of events in subsequent cycles. Clinical prediction models in patients with lymphoma not receiving prophylactic G-CSF have suggested that significant predictors of neutropenic complications (neutrophil count below 0.5×10^9/l, FN episode, dose reduction or delay) are high lactate dehydrogenase levels, high levels of tumor necrosis factor receptor and bone marrow involvement [32–34].

A composite scoring model based on the number of significant conditional predictors has been developed [13] and is illustrated in Figure 2. Higher scores (1 point each for age above 65 years, first-cycle neutrophil count nadir below 0.5×10^9/l, first-cycle FN and first-cycle hemoglobin decrease over 1 g/dl) are linked to a higher cumulative risk of subsequent neutropenic complications through four cycles of chemotherapy. An increased composite score was a strong predictor for the development of both FN and neutropenic complications.

Fig. 2



A composite scoring model to predict FN and neutropenic complications. Reproduced with permission from [13].

Guidelines for the management of neutropenia

Clinical practice guidelines have been published to facilitate the appropriate targeting of prophylactic G-CSF therapy to those patients most at risk of neutropenia, while preserving cost-effectiveness. Guidelines provided by ASCO [6], ESMO [7] and the European Organization for the Research and Treatment of Cancer (EORTC) [35] recommend primary prophylactic G-CSF in patients receiving myelosuppressive chemotherapy with an expected incidence of FN of 40% or greater. Additionally, patients at high risk of chemotherapy-induced infectious complications should be considered. Secondary prophylaxis is recommended in patients who experience an episode of FN in an earlier cycle of chemotherapy. Additionally, secondary prophylaxis is recommended in patients who cannot have their chemotherapy dose reduced, such as those who have had infections or neutropenia that exceeded 7 days during the first course of chemotherapy [35].

The National Comprehensive Cancer Network (NCCN) guidelines [36] recommend routine prophylactic G-CSF or granulocyte macrophage CSF in patients aged 70 years or older receiving CHOP (vincristine, doxorubicin, prednisone, cyclophosphamide) or similar chemotherapy, and for patients aged 60 years or older receiving induction or consolidation chemotherapy for acute myeloid leukemia. These guidelines support the suggestion that age, by itself, is not a contraindication to cancer chemotherapy. Elderly patients may benefit from treatment options sometimes reserved for younger patients, if adequate hematopoietic support is provided.

Pharmacoeconomics of managing neutropenia

In a US study of over 60 000 FN episodes in more than 40 000 patients (between 1995 and 2000), the total costs associated with FN were more than US$1 billion and FN accounted for more than 600 000 days in hospital [37]. However, when considering the economic impact of neutropenia management, it is important to consider that the majority of neutropenic patients in the US are treated as inpatients, in stark contrast to the more common European approach of outpatient treatment.

Economic analyses by the Awareness of Neutropenia in Chemotherapy Group have concluded that the risk threshold for cost-effective G-CSF should be lower than the 40% level recommended in the clinical guidelines described above. Analysis using updated, fixed and variable costs of hospitalization concluded that G-CSF primary prophylaxis will reduce the cost of care when the risk of FN is approximately 20%, hospital costs are high or an increased length of stay is expected [1]. Additionally, in an analysis incorporating direct hospitalization costs, patient out-of-pocket expenses and indirect costs, it was concluded that the risk threshold for cost-effective use of prophylactic G-CSF is between 15 and 20%. The impact of neutropenia on QoL may suggest the use of G-CSF at even lower thresholds [38].

Development of a new, sustained-duration CSF

The identification of those patients at the greatest risk of serious neutropenic complications enables physicians to proactively target the most efficacious therapies to the most vulnerable. This may prove very useful as new, cutting-edge therapies enhance the treatment choices available to the physician.

Pegfilgrastim—a novel, sustained-duration form of filgrastim (recombinant human G-CSF)—has been developed by the conjugation of a polyethylene glycol molecule to the N-terminal of the filgrastim protein. Pegfilgrastim has a much longer serum half-life than filgrastim [39] allowing once-per-chemotherapy-cycle administration. Furthermore, pegfilgrastim has a 'self-regulating' and saturable neutrophil-mediated clearance mechanism [39].

Two randomized, phase 3 trials compared pegfilgrastim with filgrastim in patients receiving chemotherapy for breast cancer. Pegfilgrastim was shown to reduce the incidence and duration of severe neutropenia to a level that was at least equivalent to that seen in the filgrastim group. Furthermore, compared with conventional G-CSF, pegfilgrastim has the additional benefits of once-per-chemotherapy-cycle, fixed-dose administration [3,40].

Further analysis of the data from these phase 3 studies was undertaken to clarify the effect of pegfilgrastim on the incidence of FN [41]. Data were pooled from both of the phase 3 studies to allow more robust comparisons

between the filgrastim and pegfilgrastim groups. The risk of FN was significantly lower (11 versus 19%; $p < 0.05$) in the once-per-chemotherapy-cycle pegfilgrastim group compared with the daily filgrastim group. The authors concluded that a single dose of pegfilgrastim was significantly more effective at reducing the overall incidence of FN than daily injection of filgrastim in patients receiving myelosuppressive chemotherapy.

Conclusions

Neutropenia is a serious and common complication of cancer chemotherapy, often occurring in the first cycle of chemotherapy. Neutropenia puts patients at risk of life-threatening infection or treatment failure because their chemotherapy dose is reduced or delayed. Neutropenia may also decrease patient QoL and increase health care costs.

Prophylactic administration of G-CSF to cancer patients receiving chemotherapy helps to manage neutropenia and allows planned doses of chemotherapy to be given on time. Clinical models that assess the risk of FN and neutropenic complications can help target G-CSF at patients who are most at risk of neutropenia and would therefore gain maximum benefit from hematopoietic support.

ASCO, ESMO and EORTC guidelines recommend prophylactic use of G-CSF in patients receiving chemotherapy when the expected risk of FN is 40% or greater. However, updated analyses by the Awareness of Neutropenia in Chemotherapy Group suggest that it would be appropriate to lower this 40% risk threshold to a value of 15 or 20%.

Pegfilgrastim, a sustained-duration form of filgrastim, has recently been developed and combines efficacy that is at least as good as traditional G-CSF treatment with the added convenience of once-per-chemotherapy-cycle administration. Pegfilgrastim provides clinicians with a valuable new tool for managing neutropenia that will also allow patients to benefit from a simple administration schedule.

References

1 Lyman GH, Kuderer N, Greene J, Balducci L. The economics of febrile neutropenia: implications for the use of colony-stimulating factors. *Eur J Cancer* 1998; **34**:1857–1864.

2 Holmes FA, O'Shaughnessy JA, Vukelja S, *et al.* Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002; **20**:727–731.

3 Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; **64**:328–340.

4 Meza L, Baselga J, Holmes FA, Liang B, Breddy J. Incidence of febrile neutropenia (FN) is directly related to duration of severe neutropenia (DSN) after myelosuppressive chemotherapy. *Proc Am Soc Clin Oncol* 2002; **21**: 255b (abstr 2840).

5 Chang J. Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. *Eur J Cancer* 2000; **36**(**suppl 1**):S11–S14.

6 Ozer H, Armitage JO, Bennett CL, *et al.* 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol* 2000; **18**:3558–3585.

7 ESMO. ESMO recommendations for the application of haematopoietic growth factors (hGFs). *Ann Oncol* 2001; **12**:1219–1220.

8 Björkholm M, Ösby E, Hagberg H, *et al.* Randomized trial of r-metHu granulocyte colony-stimulating factor (G-CSF) as adjunct to CHOP or CNOP treatment of elderly patients with aggressive non-Hodgkin's lymphoma. *Blood* 1999; **94**(**suppl 1**):599a (abstr 2665).

9 Roy E, Smith RE, Brown AM, *et al.* Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-26. *J Clin Oncol* 1999; **17**:3403–3411.

10 Le Chevalier T, Monnier A, Douillard JY, *et al.* Docetaxel (Taxotere) plus cisplatin: an active and well-tolerated combination in patients with advanced non-small cell lung cancer. *Eur J Cancer* 1998; **34**:2032–2036.

11 Crawford J, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991; **325**:164–170.

12 Chrischilles E, Delgado DJ, Stolshek BS, Lawless G, Fridman M, Carter WB. Impact of age and colony-stimulating factor use on hospital length of stay for febrile neutropenia in CHOP-treated non-Hodgkin's lymphoma. *Cancer Control* 2002; **9**:203–211.

13 Agboola O, Crawford J, Dale DA, *et al.* Risk models for neutropenic complications associated with breast cancer adjuvant chemotherapy. *Proc Am Soc Clin Oncol* 2002; **21**: 66a (abstr 261 and poster 261).

14 Gomez H, Hidalgo M, Casanova L, *et al.* Risk factors for treatment-related death in elderly patients with aggressive non-Hodgkin's lymphoma: results of a multivariate analysis. *J Clin Oncol* 1998; **16**:2065–2069.

15 Fortner B, Stolshek B, Tauer K, *et al.* Final analysis: chemotherapy-induced neutropenia (CIN) is associated with lower quality of life (QoL) in patients (pts) with cancer. *Ann Oncol* 2002; **13**(**suppl 5**):174.

16 Calhoun E, Chang C-H, Welshman E, Cella D. A neutropenia-specific quality of life instrument: Rationale for the development of the FACT-N. *Proc Am Soc Clin Oncol* 2002; **21**: 375a (abstr 1498).

17 Bonadonna G, Valgussa P. Dose–response effect of chemotherapy in breast cancer. *N Eng J Med* 1981; **304**:10–15.

18 Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med* 1995; **332**: 901–906.

19 Lepage E, Gisselbrecht C, Haioun C, *et al.* Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: application to LNH-87 protocol. The GELA (Groupe d'Etude des Lymphomes de l'Adulte). *Ann Oncol* 1993; **4**:651–656.

20 Pettengell R, Gurney H, Radford JA, *et al.* Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992; **80**:1430–1436.

21 Leonard R, Miles D, Thomas R, Nussey F. The impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. *Br J Cancer* 2003; submitted.

22 Klastersky J. Current attitudes for therapy of febrile neutropenia with consideration to cost effectiveness. *Curr Opin Oncol* 1998; **10**:284–290.

23 Kerr K. The prophylaxis of bacterial infections in neutropenic patients. *J Antimicrob Chemother* 1999; **44**:587–591.

24 Dale D. Management of febrile neutropenia: the shift from treatment to prevention. *Oncol Spectrums* 2002; **3**:6–7.

25 Bodey G, Elting L, Kassamali H, Lim B. *Escherichia coli* bacteria in cancer patients. *Am J Med* 1986; **81**:85–95.

26 Trillet-Lenoir V, Green J, Manegold C, *et al.* Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993; **29a**:319–324.

27 de Graaf H, Willemse PH, Bong SB, *et al.* Dose intensity of standard adjuvant CMF with granulocyte colony-stimulating factor for premenopausal patients with node-positive breast cancer. *Oncology* 1996; **53**:289–294.

28 Cappozzo C. Predicting the risk of neutropenic complications in patients treated with adjuvant chemotherapy for early-stage breast cancer. Presented at the *27th Annual ONS Congress*, Washington, DC, 2002.

29 Lyman GH, Crawford J, Dale D, *et al.* Clinical prediction models for febrile neutropenia (FN) and relative dose intensity (RDI) in patients receiving adjuvant breast cancer chemotherapy. *Proc Am Soc Clin Oncol* 2001; **20**: 349a (abstr 1571).

30 Lyman GH, Morrison VA, Dale D, *et al.* Risk of first febrile neutropenia (FN) among patients receiving CHOP chemotherapy. *Proc Am Soc Clin Oncol* 2002; **21**: 358a (abstr 1430).
31 Silber JH, Fridman M, DiPaola RS, Erder MH, Pauly MV, Fox KR. First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. *J Clin Oncol* 1998; **16**: 2392–2400.
32 Intragumtornchai T, Sutheesophon J, Sutcharitchan P, *et al.* A predictive model for life-threatening neutropenia and febrile neutropenia after the first course of CHOP chemotherapy in patients with aggressive non-Hodgkin's lymphoma. *Leuk Lymph* 2000; **37**:351–360.
33 Voog E, Bienvenu J, Warzocha K, *et al.* Factors that predict chemotherapy-induced myelosuppression in lymphoma patients: role of the tumour necrosis factor ligand–receptor system. *J Clin Oncol* 2000; **18**: 325–331.
34 Weiner N, Fridman M, Steinberg D, *et al.* A model to predict chemotherapy-related neutropenic events in intermediate and high grade lymphoma (IHL) patients (PTS). *Blood* 1998; **92**(**suppl 1**): 88a (abstr 361).
35 Croockewit AJ, Bronchud MH, Aapro MS, *et al.* A European perspective on haematopoietic growth factors in haemato-oncology: report of an expert meeting of the EORTC. *Eur J Cancer* 1997; **33**:1732–1746.
36 Balducci L, Yates J. General guidelines for the management of older patients with cancer. *Oncology* 2000; **14**:221–227.
37 Kuderer N, Cosler L, Crawford J, Dale D, Lyman G. Cost and mortality associated with febrile neutropenia in adult cancer patients. *Proc Am Soc Clin Oncol* 2002; **21**: 250a (abstr 998).
38 Cosler L, Agboola O, Calhoun E, Lyman G. An updated risk threshold model for G-CSF prophylaxis use in cancer chemotherapy: Incorporation of patient out-of-pocket and indirect costs. Presented at the 7*th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research*, Arlington, VA, 2002.
39 Johnston E, Crawford J, Blackwell S, *et al.* Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000; **18**:2522–2528.
40 Green MD, Koelbl H, Baselga J, *et al.* A randomized, double-blind, phase 3 study of fixed-dose, single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol* 2003; **14**:29–35.
41 Siena S, Piccart M, Holmes FA, Glaspy J, Hackett J, Renwick J. A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily Filgrastim in patients with stage II–IV breast cancer. *Oncol Rep* 2003; **10**:715–724.