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Managing myelotoxicities of breast cancer chemotherapies: what is the role for G-CSF?

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ABSTRACT

The treatment of breast cancer with chemotherapy frequently causes myelotoxicity, particularly neutropenia. Although sometimes asymptomatic, this can cause significant toxicity to the patient, and lead to difficulty in delivering the planned, optimal doses of treatment. Administration of reduced dose-intensity chemotherapy compromises treatment efficacy and may negatively impact outcomes, such as survival. Furthermore, febrile neutropenia (FN), a complication of neutropenia that can occur in the first or subsequent cycles of chemotherapy, often needs in-patient treatment (increasing the burden on healthcare resources) and can be life-threatening. Prevention of FN, its complications and maintenance of the delivery of full-dose standard and dose-dense chemotherapy regimens are therefore essential, and can be achieved with granulocyte colony-stimulating factor (G-CSF) administration. The use of antibiotic prophylaxis may not be as efficient as G-CSF for preventing FN and is not widely recommended. This article explores the role of G-CSF in managing chemotherapy-induced neutropenia in breast cancer.

1. Introduction

Chemotherapy targets rapidly proliferating cells so it is not surprising that myelotoxicity is a side effect of treatment. For many cytotoxic agents, bone marrow suppression was one of the toxicities that defined the maximum clinically deliverable doses. The myelotoxic effects of chemotherapy include neutropenia, anaemia and thrombocytopenia. Of these, neutropenia is the most common.

Despite the problems associated with neutropenia, its occurrence may indicate that chemotherapy is working effectively. In an audit of breast cancer patients treated in the South-East of Scotland with adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) between 1984 and 1998, those with grade 2 or 3 neutropenia had an improvement in overall survival (OS) of approximately 10% compared with patients who had grade 0, 1 or 4 neutropenia (overall 5-year survival: 82% [grade 2 or 3] and 68% [grades 0, 1, and 4]; $P < 0.0001$) (Fig. 1).[1] Similar data have been reported from other studies of chemotherapy delivery, for example in Canada and Finland.[2,3]

However, neutropenia and associated events are a common cause of chemotherapy dose reductions or dose delays resulting in suboptimal therapy and compromised patient outcomes. This article will focus on the incidence and consequences of neutropenic events in breast cancer patients. In addition, the roles for granulocyte colony-stimulating factor (G-CSF) and/or antibiotic prophylaxis in the management of neutropenia, as a means to enable delivery of the planned chemotherapy dose, will be addressed.

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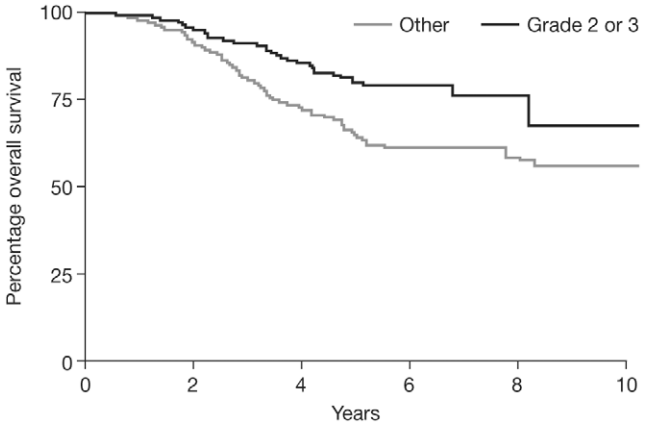

Fig. 1 – Effect of neutropenia on adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil).[1] Reprinted by permission from Macmillan Publishers Ltd: [*British Journal of Cancer*] (2003;89:1387–42), (© 2003 Cancer Research UK).

2. Incidence of neutropenia and febrile neutropenia in breast cancer patients

The true incidence of neutropenia is not known, since the nadir of the absolute neutrophil count is not routinely measured in either clinical practice or trials. Its incidence varies depending on the type and schedule of chemotherapy regimen used,[4] occurring most often with taxane-based regimens (those including docetaxel or paclitaxel).

In patients receiving CMF (n = 302)[5] or the anthracycline-based regimen FEC (5-fluorouracil, epirubicin and cyclophosphamide) (n = 996),[6] the incidences of grade 3/4 neutropenia have been reported as 1.8% and 20%, respectively. With doxorubicin and paclitaxel combination therapy[7] or a combination of carboplatin and paclitaxel[8] incidences of neutropenia as high as 79% and 82%, respectively, have been observed.

Febrile neutropenia (FN) is a serious consequence of neutropenia. FN is usually defined as a single oral temperature of ≥38.5°C or a temperature of ≥38.0°C for ≥1 h, and a neutrophil count of <500 cells/mm^3, or a count of <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3.[9] Thus, the risk of FN depends on the depth and duration of neutropenia.[10] For breast cancer chemotherapy regimens, reported incidences of FN were 4% with CAF (cyclophosphamide, doxorubicin, 5-fluorouracil),[7] 14% with FEC (500 mg/m^2, 100 mg/m^2, 500 mg/m^2) followed by docetaxel (75 mg/m^2),[11] 24.7% with TAC (docetaxel, doxorubicin, cyclophosphamide)[12] and 38% with docetaxel (100 mg/m^2) alone.[13] In a prospective, observational, European study of breast cancer therapies in the adjuvant/neoadjuvant setting (anthracycline-based 76%; anthracycline- and taxane-containing 19%; CMF-based 5%), the overall FN rate was approximately 5%.[14]

A comprehensive list of the FN risk (proportion of patients with FN in published trials) associated with common chemotherapy regimens for breast cancer is provided in the recent European Organisation for Research and Treatment of Cancer (EORTC) guidelines for G-CSF use.[4] The risk of FN also varies depending on the chemotherapy cycle, with more than 50% of initial FN episodes occurring in the first cycle. For example, in breast cancer patients, the proportion of initial episodes of FN was 58% in cycle 1.[15]

Neutropenic 'events' such as FN occur regularly and have been more consistently reported in studies than the overall incidence of neutropenia. FN results in morbidity and can be life-threatening.[6,16] Other myelotoxicities, anaemia and thrombocytopenia, occur at a much lower incidence than neutropenia and their associated complications are less frequent and usually less serious. Table 1 compares the myelotoxicity of some commonly used breast cancer chemotherapy regimens.[17–26]

Table 1 – Myelotoxicity of common chemotherapy regimens in breast cancer

Regimen	Incidence of grade 3/4 toxicity (%)		
	Neutropenia	Anaemia	Thrombocytopenia
AC[17]	81	NR	8
AC → T (paclitaxel)[18]	12	0	0
AC → T (docetaxel)[19]	88	NR	0
AT (docetaxel)[20]	13	1.4	1.4
AT (paclitaxel)[17]	89	NR	7
A → T (docetaxel)[20]	11	1.3	2.6
A/Vinorelbine[21]	87	7	2
Capecitabine/docetaxel[22]	16	<5	<5
CMF[23]	60	NR	3.7
EC[24]	78	51	33
FAC[25]	65	7	3
FEC 50[26]	11	0	NR
FEC 100[26]	25	0.8	NR
T (docetaxel)[22]	15	<5	<5
T (docetaxel) → AC[19]	100	NR	0

Abbreviations: A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, fluorouracil; M, methotrexate; T, taxane (docetaxel or paclitaxel); NR, not reported.

3. Consequences of neutropenia and associated events

Neutropenia-associated events can have significant consequences. FN can necessitate chemotherapy dose delays or dose reductions.[27,28] These events are associated with suboptimal patient outcomes.[29,30] Furthermore, neutropenia-associated events can increase the burden on healthcare resources.[9,16,31]

An audit between 1997 and 1999 of patients (n = 422) treated in the UK for primary breast cancer receiving adjuvant chemotherapy assessed the incidence of neutropenic events and their impact on clinical practice.[28] A neutropenic event was defined as hospitalisation due to FN, or a dose delay of ≥1 week and/or dose reduction of ≥15% due to neutropenia. Neutropenic events had a significant impact on the ability to deliver scheduled chemotherapy dose intensity (i.e. relative dose intensity [RDI]). Of the neutropenic patients, only 40% of 64 subjects receiving CMF and 32% of 44 patients on anthracycline-based regimens did not receive ≥85% of their planned RDI. With CMF-based regimens, the overall incidence of subjects with neutropenic events was 29%, and dose delays due to neutropenia accounted for 23% of these events.[28] The incidences of dose reduction and hospitalisation with CMF were 8% and 5%, respectively. Similarly, anthracycline-based regimens resulted in an overall incidence of 28% for neutropenic events. Neutropenia-induced dose delay occurred in 21% of patients, while 8.5% and 5.5% of patients were hospitalised or experienced dose reduction, respectively.[28] In this audit, the rate of hospitalisation for CMF-based regimens (range 1–8%) was generally lower than that for anthracycline-based regimens (0–29%) and tended to reflect the use of dose delays and/or dose reductions to manage FN.[28]

In a study examining variations in chemotherapy use and delivery and the incidence of complications in community practice settings, 45% of early-stage breast cancer patients (n = 1111) receiving adjuvant chemotherapy experienced at least one dose delay or dose reduction.[27] Most of these delays (58%) and reductions (53%) were neutropenia-related.[27]

There has been a tradition for some oncologists to reduce chemotherapy doses to avoid neutropenia. However, this practice is misguided and non-scientific,[32] since several studies that have looked at the consequences for patients receiving less than the planned regimen dose of chemotherapy have reported poorer outcomes for such patients. In a 30-year follow up of breast cancer patients (n = 386) treated with adjuvant CMF (n = 207), patients who received optimal doses of chemotherapy (≥85% of the planned dose) had the best long-term survival at 28.5 years (relapse-free survival [RFS] 42%; OS 40%) compared with those who received <85% planned dose (RFS 26%; OS 21%).[29] Similarly, a 9-year follow-up by the Cancer and Leukemia Group B demonstrated superior disease-free survival (DFS) OS for patients with breast cancer (n = 1550) who received moderate- or high-dose CAF chemotherapy compared with those who received a low-dose regimen ($P < 0.0001$ and $P = 0.004$, respectively).[33] In this trial the 5-year survival rates (95% confidence interval [CI]) for the low-, moderate- and high-dose groups, respectively, were as follows: OS: 72% (68–75%), 77% (74–81%), 78% (75–82%); DFS: 56% (51–60%), 61% (57–65%), 66% (62–70%).[33] Recently, Chirivella et al. reported that dose delays or reductions significantly decreased the 10-year survival rates in early-stage breast cancer patients (n = 1056) receiving anthracycline non-taxane-based chemotherapy.[30] The event-free survival rates were 75.8% and 59.3% for patients who received ≥95% RDI or <95% RDI, respectively. With regards to OS, the rates were 84.2% (≥95% RDI) and 73.9%, respectively.[30] Furthermore, a Swedish study that aimed to increase the dose of adjuvant FEC chemotherapy in order to deliver a pre-defined level of neutropenia found this approach to give better survival than high-dose chemotherapy.[34]

Studies have shown that FN accounts for a large proportion of healthcare expenditure and hospitalisations in breast cancer patients receiving adjuvant chemotherapy.[31] In a US-based multicentre study of 41,779 cancer patients hospitalised with FN, overall (i.e. all patients) in-hospital mortality was 9.5% (± 0.3% 95% CI)[16]; although specifically in breast cancer (early and metastatic) patients the in-hospital mortality due to FN was 3.6 ± 0.7%.[16] In the National Epirubicin Adjuvant Trial (NEAT), in which 1009 patients were treated with epirubicin + CMF and 1012 patients received CMF, there were only 18 chemotherapy-related deaths and only 8 of these (four in each group) were due to neutropenic sepsis.[35] In the Kuderer et al. analysis, the mean and median length of stay for all FN-related hospitalisations were 11.5 days and 6 days, respectively.[16] Furthermore, 35% of cases involved hospitalisation for ≥10 days, accounting for 78% of overall hospital costs. The mean and median costs of hospitalisation were $19,110 and $8,376, respectively, placing a large burden on healthcare resources. European costs are more difficult to estimate, but one study from Edinburgh has suggested that each episode costs the NHS between £1500 and £3776 (Personal communication: Heather Dalrymple, WGH Pharmacy, Edinburgh).[36]

4. Management of neutropenia

If chemotherapy-induced neutropenia is indicative for a survival benefit, but in itself results in toxicity and possible death, how can we maintain the efficacy whilst reducing the morbidity and mortality associated with adjuvant chemotherapy? The answer seems to be by ensuring dose delivery on time (or even increasing dose intensity) to maintain the anti-cancer effects, and reducing the toxicity on the bone marrow.

4.1. *Role of prophylactic G-CSF*

4.1.1. *Guidelines for use of G-CSFs*

The likelihood of developing myelotoxicity, and its severity, is dependent on the chemotherapy regimen used and individual patient risk factors. FN risk associated with different regimens and guidelines for the appropriate use of G-CSFs are detailed in the EORTC G-CSF guidelines.[4]

EORTC guidelines recommend prophylactic G-CSF if the overall FN risk of a particular regimen is ≥20%. For regimens with a 10–20% FN risk, patient risk factors must also

be assessed and prophylactic G-CSF used as appropriate. A major patient-related factor that affects FN risk is age, with patients ≥65 years having an increased FN risk. Other factors include poor performance status, advanced disease or a previous episode of FN.

The guidelines also state that G-CSF use should be governed by the intent of chemotherapy, whether it is curative, for prolongation of survival or palliation. If a decrease in the RDI or dose density of a chemotherapy regimen compromises survival, the guidelines recommend that primary prophylaxis with G-CSF should be given to maintain appropriate dosing levels. In other cases where survival is not affected by the treatment delivery, an alternative, less myelosuppressive regimen or dose modification should be considered. Interestingly, the EORTC guidelines are very similar to those of the American Society of Clinical Oncology[37] and the National Comprehensive Cancer Network,[38] indicating the consistency of the available published data.

The choice of G-CSF formulation (filgrastim [Neupogen®], lenograstim [Granocyte®] or pegfilgrastim [Neulasta®] was not specified in the EORTC guidelines, since they are all efficacious for the prevention of FN and its complications.[4] However, recent studies have highlighted that there may be added benefits for patients receiving pegfilgrastim compared to daily dosing G-CSFs. Pegfilgrastim is at least as effective as filgrastim but has a sustained duration of action allowing once per cycle dosing.[39] This less frequent dosing schedule is believed to reduce the burden of numerous medical visits for the patient, which may have an impact on compliance and quality of life.[39] In breast cancer patients receiving docetaxel, the first- and subsequent-cycle use of pegfilgrastim significantly reduced the incidence of FN (1%) compared with placebo control (17%; $P < 0.001$; difference between percentages = –15.5, 95% CI = –19.0, –11.9).[40] Similarly, pegfilgrastim reduced the FN incidence (6%) compared with daily G-CSF (17%; $P < 0.001$) in breast cancer patients treated with TAC.[41]

4.1.2. *Use of G-CSFs for elderly patients*

The administration of standard chemotherapy in elderly and frail patients remains particularly difficult, not only because of diminished marrow reserves leading to increased toxicity, but also because of the presence of comorbidities.[42] Often, there is a defeatist attitude towards chemotherapy in such patients. Consequently, these individuals may not receive curative regimens or maximal doses because the risk of ensuing toxicities is considered too great. A review of studies in elderly patients with breast cancer concluded that otherwise healthy patients can and should receive the same standard adjuvant chemotherapy as younger patients and that G-CSF prophylaxis to ameliorate chemotherapy-induced neutropenia helps to maintain total dose and optimal RDI.[43] Furthermore, prophylactic use of G-CSFs in elderly patients enabled the administration of planned doses of chemotherapy at the scheduled time.[42] These data have led to EORTC guidelines for use of G-CSF in elderly cancer patients.[44]

4.1.3. *G-CSF support of planned RDI*

As discussed previously standard doses of chemotherapy are associated with various degrees of neutropenia and FN; both of which can lead to dose delays and/or dose reductions reducing the RDI. The RDI is the ratio between the delivered dose of a drug in a given time and the planned dose of that drug over the same time interval. G-CSFs can be used for the management of chemotherapy-induced neutropenia to enable the delivery of the planned dose of chemotherapy, thus, maintaining the RDI for optimal patient outcomes.

In a study of CMF therapy, patients with insufficient leukocyte recovery either received G-CSF ($n = 50$) or no G-CSF support ($n = 22$).[45] The proportion of patients in the G-CSF group who received a RDI ≥85% was 74% compared with 45% in the 'no G-CSF' group ($P < 0.05$). In a recent community practice study, involving over 2000 cancer patients (46% with breast cancer), first- and subsequent-cycle pegfilgrastim use enabled 97.1% and 97.9% of patients to receive full dose chemotherapy and treatment on schedule, respectively.[46]

Despite compelling evidence for their use to help maintain delivery of optimal RDI of chemotherapy, administration of G-CSF may occur infrequently (<6%) in clinical practice.[28] Furthermore, in this review of clinical practice ($n = 422$), G-CSF support was administered 'reactively' either to seven hospitalised patients to treat FN (1.7%) or to 15 non-hospitalised patients as secondary prophylaxis to avoid further complications following a neutropenic event in a previous cycle (3.6%).

4.1.4. *Dose-dense chemotherapy and G-CSFs*

As outcomes are closely linked to chemotherapy dose, one strategy to increase efficacy has been to increase dose levels. For many years, there was great interest in the use of high doses of chemotherapy, supported by bone marrow or bone marrow stem cell auto-transplant. However, the majority of these studies showed that these strategies did not confer additional benefits for patients over and above optimal conventional chemotherapy.

More recently, there have been studies increasing the dose density of sequential chemotherapy agents. This strategy is promising since dose density can be increased or maintained while toxicity is unchanged,[18] by using GCSF to accelerate recovery of neutrophil levels to permit cycles being given at 2-weekly intervals, rather than conventional 3-weekly intervals. In a 2×2 randomised study of over 2000 women with breast cancer, those patients given concurrent doxorubicin and cyclophosphamide, followed by paclitaxel, at 2-weekly intervals supported with daily filgrastim had significantly improved DFS and OS compared to those women with conventional 3-week dosing (Fig. 2).[18] The dose-dense regimen was also associated with a reduced frequency of severe neutropenia compared with the conventional regimen.

An interim analysis from a Canadian randomised trial (NCIC CTG MA.21) comparing CEF (cyclophosphamide (C), epirubicin (E) and fluorouracil (F) with dose-dense EC/T (E and C followed by a taxane [T]) or standard AC/T (doxorubicin [A]) found AC/T to be inferior to CEF or EC/T in terms of relapse-free survival in high-risk operable breast cancer.[47] However, the authors conclude that it is still too early to detect any difference between CEF and dose-dense EC/T so a dose-dense approach may still add benefit in this setting.

The EORTC guidelines recommend that G-CSF support is mandatory to the administration of dose-dense chemo-

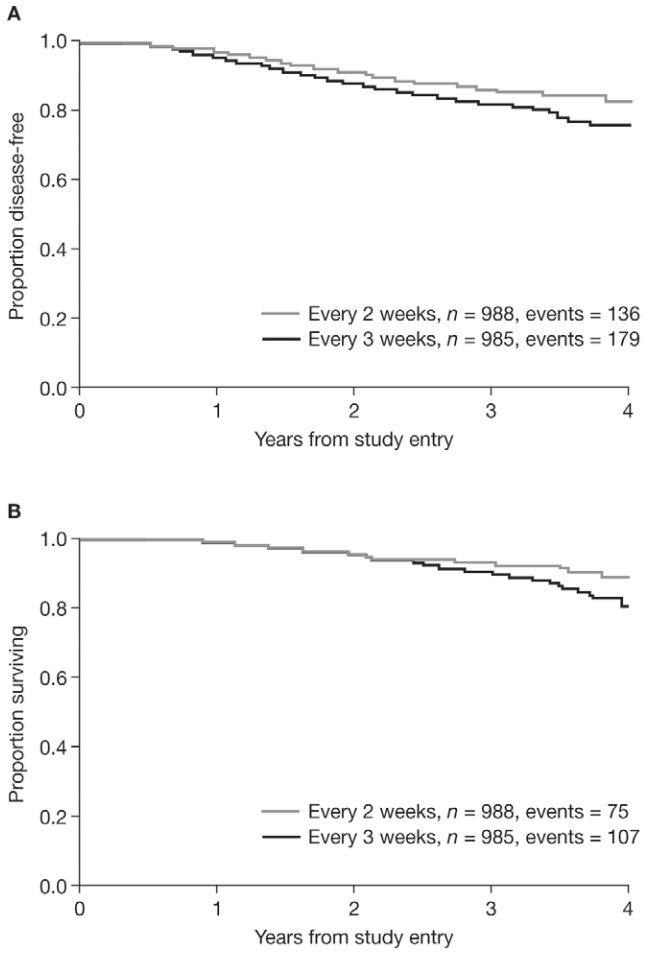

Fig. 2 – Disease-free survival (a) and overall survival (b) in patients receiving filgrastim plus chemotherapy (doxorubicin, cyclophosphamide, paclitaxel) administered every 2 weeks compared with chemotherapy alone every 3 weeks. Reprinted with permission from the American Society of Clinical Oncology from: Citron ML, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *Journal of Clinical Oncology* 2003;21:1431–9.[18]

therapy regimens.[4] In a meta-analysis of eight randomised controlled trials (n = 1444) G-CSF use was associated with a significantly reduced risk of FN (odds ratio 0.38; 95% CI: 0.29–0.49; P = 0.001) compared with no G-CSF in patients receiving dose-intensive chemotherapy regimens.[48] The risks of documented infection and infection-related mortality were also reduced with G-CSF administration.

4.2. *Role of prophylactic antibiotics*

Inevitably, chemotherapy-induced myelosuppression causes an increased incidence of infection, including bacterial infections, which lead to complications associated with treatment of the malignancy, the need for hospitalisation, increased burden on resources and, in some cases, death.[49] In a study of over 1500 patients receiving chemotherapy for solid tumours or lymphoma without prophylactic G-CSF support (of whom 35% had breast cancer), prophylactic levofloxacin significantly decreased the incidence of febrile episodes over the entire course of chemotherapy (10.8% versus 15.2%; P = 0.01; relative risk 0.71, 95% CI 0.55–0.92) and reduced the rate of hospitalisations for infections (15.7% versus 21.6%; P = 0.004; relative risk 0.73, 95% CI 0.59–0.90) compared with placebo.[49]

A recent meta-analysis of 95 randomised, controlled trials in neutropenic patients receiving cytotoxic treatment showed significantly decreased risk for death with prophylactic antibiotics compared with placebo or no intervention (relative risk 0.67; 95% CI: 0.55–0.81).[50] Mortality was substantially reduced when the analysis was limited to studies involving the use of fluoroquinolones.

There are increasing concerns about the overuse of antibiotics leading to an increase in the incidence of antibiotic resistance, which is particularly problematic in immunocompromised patients (such as those receiving myelosuppressive chemotherapy). According to the EORTC G-CSF guidelines, routine antibiotic prophylaxis is not recommended.[4] Mortality from adjuvant chemotherapy of breast cancer is extremely low, so the impact of poor dose delivery remains the more serious issue for the patient.

4.3. *Prophylaxis with G-CSF and antibiotics*

As described above, there are two alternative approaches to maintaining chemotherapy dose while reducing toxicity: the use of prophylactic G-CSF or fluoroquinolones. Can we thus benefit patients more by combining these two approaches? There is some evidence that using both strategies may give additional benefit in some specific situations like TAC chemotherapy. In a study comparing the efficacy of pegfilgrastim, with (n = 219) or without (n = 311) ciprofloxacin, the antibiotic had little impact on pegfilgrastim's efficacy in reducing the FN incidence (5% versus 6%), but there were fewer hospitalisations (161 versus 210), fewer anti-infective administrations (25 versus 44) and the rate of severe infections was reduced from 4% to 1% with the addition of ciprofloxacin to pegfilgrastim. Use of ciprofloxacin in addition to a G-CSF is therefore a standard regimen in Germany where TAC chemotherapy is used, based on these data from a German study.[41]

5. Conclusions

Maintenance of the dosing schedule – and thus the RDI – of chemotherapy is vital in the adjuvant treatment of breast cancer in order to maximise survival. Chemotherapy-induced myelosuppression, including neutropenia and FN, can cause disruption of the dosing schedule until neutrophil levels are restored and/or infections resolve. Administration of G-CSF is effective in reducing the risk of FN and shortening the duration of neutropenia and consequently, helps to deliver the planned dose of chemotherapy on schedule.

6. Conflict of interest statement

David Cameron has received honoraria from Amgen, Pfizer, Sanofi-Aventis, F. Hoffmann La-Roche and BMS. Matti Aapro has received grants from and serves on an Advisory Board and Speaker's Bureau for Amgen, F. Hoffmann La-Roche and Sanofi-Aventis.

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REFERENCES

1. Cameron DA, Massie C, Kerr G, Leonard RC. Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer. *Br J Cancer* 2003;**89**:1837–42.
2. Mayers C, Panzarella T, Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. *Cancer* 2001;**91**:2246–57.
3. Saarto T, Blomqvist C, Rissanen P, Elomaa I. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. *Br J Cancer* 1997;**75**:301–5.
4. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;**42**:2433–53.
5. Crivellari D, Bonetti M, Castiglione-Gertsch M, et al. Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: the International Breast Cancer Study Group Trial VII. *J Clin Oncol* 2000;**18**:1412–22.
6. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol* 2006;**24**:5664–71.
7. 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. *J Clin Oncol* 2000;**18**:3558–85.
8. Perez EA. Carboplatin in combination therapy for metastatic breast cancer. *Oncologist* 2004;9:518–27.
9. Hughes WT, Armstrong D, Bodey, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;**34**:730–51.
10. Bodey GP, Buckley M, Sathe Y-S, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966;**64**:328–40.
11. Ohnoa S, Toi M, Kuroi K, et al. Update results of FEC followed by docetaxel neoadjuvant trials for primary breast cancer. *Biomed Pharmacother* 2005;**59**(suppl 2):S323–4.
12. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;**352**:2302–13.
13. Hudis CA, Seidman AD, Crown JPA, et al. Phase II and pharmacologic study of docetaxel as initial chemotherpay for metastatic breast cancer. *J Clin Oncol* 1996;**14**:58–65.
14. Jackisch C, Schwenkglens M, Leonard R, et al. INC-EU prospective observational European neutropenia study: preliminary breast cancer results. *Eur J Cancer* 2006;**Suppl 4**. abstr. 176.
15. Crawford J, Wolff D, Culakova E, et al. First cycle risk of severe and febrile neutropenia in cancer patients receiving systemic chemotherapy: results from a prospective nationwide study. *Blood* 2004;**104**. abstr. 2210.
16. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;**106**:2258–66.
17. Biganzoli B, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. *J Clin Oncol* 2002;**20**:3114–21.
18. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;**21**:1431–9.
19. Perez EA, Geeraerts L, Suman VJ, et al. A randomized phase II study of sequential docetaxel and doxorubicin/cyclophosphamide in patients with metastatic breast cancer. *Ann Oncol* 2002;**13**:1225–35
20. Alba E, Martin M, Ramos M, et al. Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: a Spanish Breast Cancer Research Group (GEICAM-9903) phase III study. *J Clin Oncol* 2004;**22**:2587–93.
21. Norris B, Pritchard KI, James K, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group study MA8. *J Clin Oncol* 2000;**18**:2385–94.
22. O'Shaughnessy J, Miles D, Svetislava V, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;**20**:2812–23.
23. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol* 1998;**16**:2651–8.
24. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. *J Clin Oncol* 2003;**21**:843–50.
25. Jassem J, Pienkowski T, Pluzanska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. *J Clin Oncol* 2001;**19**:1707–15.
26. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2001;**19**:602–11.
27. Link BK, Budd GT, Scott S, et al. Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: current patterns of care. *Cancer* 2001;**92**:1354–67.
28. Leonard RC, Miles D, Thomas R, Nussey F; UK Breast Cancer Neutropenia Audit Group. Impact of neutropenia on

delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. *Br J Cancer* 2003;**89**:2062–8.
29. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. *BMJ* 2005;**330**:217.
30. Chirivella I, Bermejo B, Insa A, et al. Impact of chemotherapy dose-related factors on survival in breast cancer patients treated with adjuvant anthracycline-based chemotherapy. *J Clin Oncol* 2006;**24**:18s. abstr. 668.
31. Mayordomo JI, Castellanos J, Pernas S, et al. Cost analysis of febrile neutropenia management of breast cancer patients in clinical practice in Spain. *Ann Oncol* 2006;**17**(suppl 9):ix190–5. abstr. 617P.
32. Norton L, Simon R. Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer Treat Rep* 1977;**61**:1307–17.
33. Budman DR, Berry DA, Cirrincione CT, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 1998;**90**:1205–11.
34. Bergh J, Wiklund T, Erikstein B, et al. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian Breast Group 9401 study. *Lancet* 2000;**356**:1384–91.
35. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med* 2006;**355**:1851–62.
36. Pettengell R, Booth P, Malin J, et al. Primary prophylaxis with pegfilgrastim was more cost-effective than filgrastim in patients with non-Hodgkin's lymphoma receiving CHOP-21 in the UK. *Presented at the 12th Congress of the European Haematology Association*, Vienna, Austria, June 7–10, 2007. abstr. 0602.
37. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;**24**:3187–205.
38. National Comprehensive Guidelines Network. Myeloid Growth Factors v.1. 2007. Available from: http://www.nccn.org. Last accessed January 12, 2007.
39. Lyman GH. Pegfilgrastim: a granulocyte colony-stimulating factor with sustained duration of action. *Expert Opin Biol Ther* 2005;**5**:1635–46.
40. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2005;**23**:1178–84.
41. von Minckwitz G, Blohmer J, Loehr A, et al. Pegfilgrastim alone or with ciprofloxacin significantly reduces febrile neutropenia and hospitalization vs GCSF alone in breast cancer patients receiving neoadjuvant chemotherapy with docetaxel/doxorubicin/cyclophosphamide (TAC). *Eur J Cancer Suppl* 2006;**4**:151. abstr. 356.
42. Rosti G, Kopf B, Cariello A, et al. Prevention and therapy of neutropenia in elderly patients. *Crit Rev Oncol Hematol* 2003;**46**:247–53.
43. Balducci L. The geriatric cancer patient: equal benefit from equal treatment. *Cancer Control* 2001;**8**(suppl 2):1–25.
44. Repetto L, Biganzoli L. Koehne CH, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* 2003;**39**:2264–72.
45. 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**:289–94.
46. Ozer H, Mirtsching B, Rader M, Ding B, Truschinski D, Dreiling L. Final results of a large, community-based, prospective study evaluating the impact of first and subsequent cycle pegfilgrastim on neutropenic events in patients receiving myelosuppressive chemotherapy. *J Clin Oncol* 2006;**24**:18s. abstr. 8569.
47. Burnell M, Levine M, Chapman JA, et al. A randomized trial of CEF versus dose dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: results of an interim analysis. *Presented at the 29th Annual San Antonio Breast Cancer Symposium*, December 14–17, 2006. abstr. 53.
48. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med* 2002;**112**:406–11.
49. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med* 2005;**353**:988–98.
50. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med* 2005;**142**:979–95.