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Treatment of Breast Cancer with Chemotherapy in Combination with Filgrastim

Approaches to Improving Therapeutic Outcome

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Abstract

Chemotherapy improves disease-free and overall survival in breast cancer, and its benefit is directly related to the percentage of the planned dose that is actually administered. In all current chemotherapeutic regimens, a substantial proportion of patients have reductions and/or delays in dosage due to side effects. In about half such cases, the delays or reductions are related to neutropenia. Overall, approximately 30% of patients have a reduction to less than 85% of the planned dosage. Women aged ≥50 years are more likely to experience a reduction or delay in dose. Dose-intense regimens (excluding myeloablative high-dose chemotherapy) which increase the dose of chemotherapy or reduce the interval between cycles, or both, are a promising approach now under investigation. The human granulocyte colony-stimulating factor filgrastim reduces the incidence of neutropenia and facilitates adherence to full dose intensity in both standard and dose-intensified regimens. A model based on the first-cycle absolute neutrophil count nadir has been developed and validated to determine which patients should receive filgrastim. A cost benefit associated with the use of filgrastim in patients with breast cancer has been realised. This may lead to a re-evaluation of the current treatment guidelines.

1. Introduction

Breast neoplasms are typically associated with significant rates of metastasis, recurrence and mortality.[1-5] Although breast cancers often require multimodal therapy, surgery remains the primary treatment in most cases. Postoperative adjuvant radiation therapy to the chest wall and regional lymph nodes is indicated in patients at high risk of local-regional failure following surgery.[6] The highest risk of local recurrence is found in patients with four or more positive axillary nodes, grossly evident extracapsular nodal extension, large primary tumours, and very close or positive deep margins of resection of the primary tumour. Adjuvant radiation therapy can decrease the risk of local-regional recurrence in this group, even among patients who receive adjuvant chemotherapy. Adjuvant chemotherapy is known to promote significantly higher survival rates among breast cancer

patients than therapeutic surgery alone.[7] In women with estrogen receptor-positive tumours, tamoxifen or other hormonal therapies have been shown to significantly improve survival.[8] Hormonal therapy is generally well tolerated, and survival benefits continue with treatment up to 5 years. In patients for whom hormonal therapy is contraindicated, several regimens using cytotoxic chemotherapy have been proved to be beneficial. The value of such adjuvant chemotherapy in decreasing the risk of recurrence and improving long-term survival is well established. A meta-analysis of randomised trials comparing combination chemotherapy and no chemotherapy reported a significant reduction in mortality and recurrence rate in patients receiving chemotherapy irrespective of nodal status (negative versus positive), estrogen-receptor status and the presence or absence of tamoxifen therapy.[8]

The chemotherapy regimens most commonly used are as follows: (i) cyclophosphamide, methotrexate, fluorouracil (CMF); (ii) doxorubicin, cyclophosphamide (AC); and (iii) cyclophosphamide, doxorubicin, fluorouracil (CAF).[9] Older patients (aged ≥65 years) are more likely to receive CMF. Doxorubicin is thought to be the single most active agent against breast cancer. The benefit of chemotherapy varies considerably with patient age and menopausal status. For all women aged <50 years at randomisation, combination chemotherapy increased 10-year survival from 71 to 78% for those with node-negative disease and from 42 to 53% for those with node-positive disease. In the group aged 50 to 69 years at randomisation, combination chemotherapy increased 10-year survival from 67 to 69% for those with node-negative disease and from 46 to 49% for those with node-positive disease.[8] In the trials in which patients received CMF of 6 to 24 months' duration, no additional survival advantage was seen with durations longer than 6 months. Regimens containing anthracyclines (e.g. doxorubicin, epirubicin) have been reported to be slightly superior to CMF.

Systemic therapy is indicated in patients with metastatic breast cancer and should be considered in patients with local recurrence because of the high risk of occult metastases. The aim of treatment in such cases is to prolong life and improve the quality of life. Median survival of patients with metastatic disease has been reported to be 18 to 24 months, but some patients experience long-term survival.[10] Factors in evaluating treatment of a patient with metastatic breast cancer include the patient's hormonal status (premenopausal or postmenopausal), estrogen receptor status of the cancer, whether the cancer has previously responded to hormonal therapy, the length of the disease-free interval, the location and extent of the metastases, and the patient's age and general health status. In addition to systemic therapy, palliative surgery and/or radiation therapy may be useful in patients with limited symptomatic metastases.

Approximately a quarter of all patients with breast cancer have tumours that overexpress the HER2/neu gene. Such patients should be considered for treatment with the monoclonal antibody trastuzumab, which binds to the HER2/neu receptor. Trastuzumab produced a response rate of 15% when administered as monotherapy to women with metastatic breast cancer.[11] Trastuzumab combined with chemotherapy was more effective than chemotherapy alone.[12] Trastuzumab is currently being evaluated in combination with docetaxel in the treatment of patients with HER2-overexpressing metastatic breast cancer. Preliminary data from a pilot study were recently reported and suggest that the combination of weekly docetaxel and trastuzumab is well tolerated and has significant antitumour activity in pretreated patients with metastatic breast cancer.[13]

The most significant obstacle to long-term survival in patients with breast cancer is tumour drug resistance.[5,14,15] This fact has spurred research into newer polychemotherapies with or without cellular support[15-19] and into methods to identify drug-resistance characteristics in primary tumours[4] or to predict metastatic potential for a given tumour type.[20] For both standard and high-dose regimens, however, the advantage of poly-

chemotherapies is gained at the cost of increased adverse effects and haematological disturbances, such as myeloablation, acute and febrile neutropenia (FN), and sequelae to therapy that include mucositis and opportunistic infections.[5,21-26]

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. It acts primarily to stimulate proliferation and differentiation of committed progenitor cells of the granulocyte-neutrophil lineage into functionally mature neutrophils. Filgrastim has been used successfully for more than a decade in the prevention of neutropenia related to myelosuppressive chemotherapy.[27] The recombinant, nonglycosylated form (filgrastim) and glycosylated form (lenograstim) are comparable in their ability to stimulate expansion and migration of precursor neutrophil granulocytes from the bone marrow into the peripheral circulation.[28,29] This drug activity permits sufficient reconstitution of neutrophil numbers and function in patients receiving standard and dose-intensive chemotherapy for a variety of neoplasms, including breast cancer.

This article reviews the pertinent literature on the haematological and cellular effects of filgrastim and its therapeutic use in reducing the incidence and duration of severe neutropenia in patients receiving breast cancer chemotherapy. The paper also examines methods of determining appropriate use of filgrastim, the use of filgrastim in dose-dense regimens and stem cell transplantation, and possible future uses, including immunotherapy in combination with monoclonal antibodies or cytokines.

2. Dose and Efficacy

In long-term follow-up (up to 20 years after surgery), a clear relationship has been observed between survival and the percentage of planned dose that breast cancer patients actually received.[30] Women who received <65% of the planned dose had relapse-free survival and overall survival rates very similar to those of controls, women who received 65 to 84% of the planned dose had slightly better rates, but those who received ≥85% of the planned dose had statistically and clinically significantly better relapse-free and overall survival (figure 1).

Adverse effects, especially neutropenia, often necessitate a delay or reduction in the chemotherapy dose. Reductions and delays in dose are common in all current cancer treatment regimens. Women aged >50 years are especially likely to

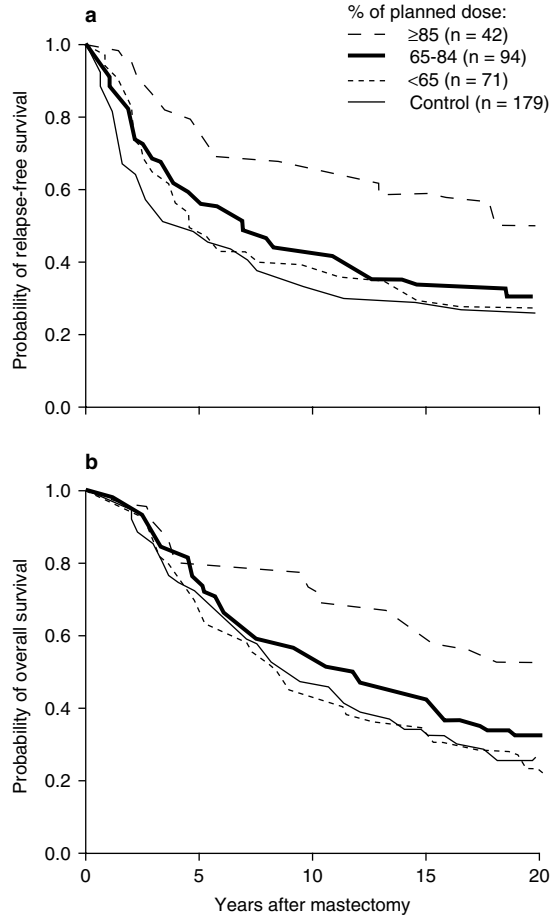


Fig. 1. Delivery of planned dose and long-term survival rates. The Milan Study: relapse-free and overall survival with CMF (cyclophosphamide, methotrexate, fluorouracil); 20-year follow-up (n = 386). (Reproduced with permission from Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med 1995; 332: 901-6.[30] Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

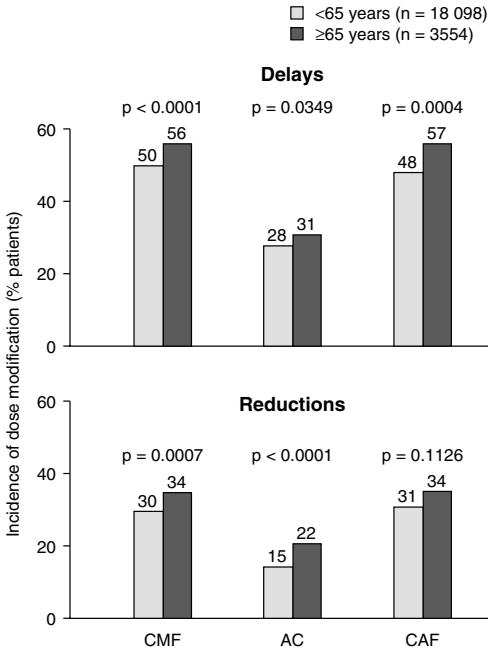


Fig. 2. Chemotherapy dose modifications by regimen and age group.[9] Chemotherapy dose modifications occur with all regimens and are more frequent in elderly patients. **AC** = doxorubicin, cyclophosphamide; **CAF** = cyclophosphamide, doxorubicin, fluorouracil; **CMF** = cyclophosphamide, methotrexate, fluorouracil.

have a low tolerance for high-dose-intensity therapy and to consequently discontinue it (figure 2). Among patients undergoing CMF therapy, 20% of those aged <65 years compared with 27% of those aged ≥65 experienced a reduction in dose intensity to <85% of the planned dosage;[9] the respective percentages were 9 and 14% among patients receiving AC and 23 and 28% in patients receiving CAF. Of 21 652 patients receiving adjuvant chemotherapy for breast cancer, 6% required intervention for FN. Overall, among more than 1100 patients with early-stage breast cancer receiving some form of combination chemotherapy, 45% experienced a reduction or a delay in dose; of these, 58% of the delays and 53% of the reductions were related to neutropenia.[31] Approximately 30% of patients overall received less than 85% of the planned dosage. A retrospective analysis was initiated to evaluate individual oncologist practice patterns, to review the selection of treatment regimens and to assess the relative dose intensity between CMF, AC and CAF.[32] As of 1999, 5819 records were analysed. Overall results indicated that 20.8% of patients received a dose intensity of <85%, 28.9% experienced dose reductions, 39.9% had a dose delay and 4.8% experienced FN. A survey of physicians disclosed that AC was regarded as being the more myelosuppressive regimen; however, results indicated that patients treated with AC experienced improved quality of treatment with fewer dose reductions or delays and a greater average dose intensity. These results indicate a substantial inconsistency between perceived toxicity and clinical actuality in the adjuvant treatment of breast cancer.

The importance of maintaining standard dose chemotherapy intensity was demonstrated in a study of 1550 patients with stage II breast cancer who were randomised within 6 weeks of surgery to receive CAF high-dose intensity (600/60/600 mg/m^2, 4 cycles), moderate-dose intensity (400/40/400 mg/m^2, 6 cycles) or low-dose intensity (300/30/300 mg/m^2, 4 cycles).[33] The high-dose arm had twice the dose intensity and twice the drug dose of the low-dose arm. The moderate-dose arm had two-thirds the dose intensity of the high-dose arm but the same total drug dose. At 5 years, overall survival was 79% for patients in the high-intensity arm, 77% for patients in the moderate-intensity arm and 72% for patients in the low-intensity arm; disease-free survival was 66, 61 and 56%, respectively. At median follow-up of 9 years, patients in the moderate- and high-dose arms had significantly longer disease-free survival ($p < 0.0001$) and overall survival ($p = 0.004$) than patients in the low-dose arm. No significant differences in disease-free or overall survival were noted between the moderate- and the high-dose arms. Multivariate analysis confirmed that dose (high/moderate *vs* low) was an independent predictor of disease-free survival (risk ratio 1.27, p =

0.0001) and overall survival (risk ratio 1.27, p = 0.0095). Haematological toxicity paralleled treatment intensity ($p < 0.01$). The incidence of grade 3 or 4 leucopenia (<1900 cells/μl) was 4% among patients receiving low-dose-intensity CAF, 17% among patients receiving moderate-dose intensity, and 66% among those receiving high-dose intensity.

Evidence for interaction of dose and expression of the HER-2/neu (c-erbB-2) gene has been reported.[34] Among patients randomised to receive CAF high dose (600/60/600 mg/m^2), moderate dose (400/40/400 mg/m^2) or low dose (300/30/300 mg/m^2), the moderate- and high-dose regimens were associated with significantly longer disease-free survival ($p < 0.01$). However, analysis by subgroups revealed that the dose response was significant in patients with overexpression of HER-2/neu but not in patients without overexpression of this gene.

2.1 Benefits of Filgrastim in Adhering to Dosage

The clinical utility of filgrastim derives from its specificity and potency of action on the neutrophil cell lineage.[35] Filgrastim directly stimulates the growth and differentiation of neutrophil progenitor cells. Adjuvant filgrastim therapy promotes recovery of normal levels of circulating neutrophils after completion of a course of chemotherapy, and it consistently decreases the incidence of FN.[36]

Numerous controlled trials have evaluated the efficacy of filgrastim in patients receiving myeloablative or high-dose chemotherapy for various solid tumours.[37-42] These studies confirmed that filgrastim is well tolerated and associated with significantly shorter hospital stays and reduced rates of FN and culture-documented infection. Improvements in overall patient survival, however, have not been observed,[39,41] thus separating the beneficial haematopoietic effects of filgrastim from the putative effects of chemotherapy on long-term cancer remission or survival. For example, initial phase II trials investigating the utility of prophylactic filgrastim in preventing neutropenia among patients receiving myelosuppressive chemotherapy for small-cell lung cancer[37,43] found that filgrastim was well tolerated and led to significant reductions in the rate of grade IV neutropenia and FN. Length of hospital stay and duration of antibiotic treatment were also significantly decreased. Similar encouraging findings have been demonstrated among women with advanced breast cancer. In a study of 44 women with metastatic disease, patients receiving filgrastim achieved an absolute neutrophil count (ANC) of at least 500/μl significantly earlier than controls and had shorter hospitalisation times, with no significant related toxicity.[44] On the basis of its successful use in breast cancer and other solid tumours, filgrastim is approved for use in the US to reduce the incidence of infection, as manifested by FN, in patients receiving myelosuppressive chemotherapy.[36] Filgrastim is the predominant cytokine used to reduce neutropenia-related complications in breast cancer patients.[45,46] In a study performed by Bergh and colleagues,[47] filgrastim demonstrated a benefit in support of higher doses of fluorouracil, epirubicin and cyclophosphamide (FEC) combination therapy. Patients were given nine courses every 3 weeks of individually dose-escalated and filgrastim-supported FEC. This customised therapy made it possible for all patients to be treated at comparable levels of haematological toxicity with significantly higher doses without a remarkable increase in other organ toxicities. Another study of premenopausal patients with node-positive breast cancer evaluated the effects of G-CSF on total dose and dose intensity of standard oral adjuvant CMF.[48] The dose intensity of the G-CSF-treated group was higher than that of controls. The authors noted an important finding in patients receiving radiotherapy: a negative effect on marrow recovery. This was significant, but not dependent on G-CSF.

By promoting rapid haematopoiesis, filgrastim administration can significantly shorten patient hospital stays and the duration of antibiotic therapy.[38,49-51] In the B-30 trial currently sponsored by the National Surgical Adjuvant Breast and

Bowel Project (NSABP), disease-free survival, overall survival and quality of life are being evaluated in patients with advanced breast cancer randomised to treatment with three combination regimens of doxorubicin and docetaxel with or without cyclophosphamide. According to preliminary results from this study, dose reduction and primary prophylaxis with filgrastim have been necessary to manage adverse haematological effects among patients in two of the three patient groups.

A recent meta-analysis of eight randomised clinical trials further demonstrated the clinical usefulness of filgrastim. In these studies, which involved 1144 patients, use of filgrastim prior to neutropenia or fever effectively reduced the incidence of FN and infection in adult patients with a variety of malignancies.[52] Similarly, adjuvant treatment with filgrastim was shown to reduce the duration of neutropenia, antibiotic treatment and infection-related hospitalisation for patients with advanced cancers receiving dose-intensive chemotherapy.[49,53] These studies confirmed that filgrastim is well tolerated and that significantly shorter hospital stays and reduced rates of FN and culture-documented infection are associated with its use. Improvements in overall patient survival, however, have been rarely observed.[52]

Filgrastim is most effective if initiated before neutropenia appears and prior to onset of microbial sepsis.[36] In clinical studies, filgrastim has been administered at different times (1 to 9 or more days) after initiating chemotherapy or at neutrophil nadir, depending on the protocol, patient population or expected outcomes.[54,55] For optimum benefit, filgrastim should be started within 72 hours of completion of chemotherapy, but it appears to work especially well in mobilising neutrophils when given earlier in the course of treatment.[56,57]

Adjuvant filgrastim therapy has particular utility among elderly patients, who are at increased risk of dose delays and reductions because of their enhanced vulnerability to chemotherapeutic adverse effects.[58] After reviewing the 2000 update of recommendations for the use of haematopoietic colony-stimulating factors,[59] Balducci and Lyman[60] suggested that patients aged ≥70 years being treated with moderately toxic chemotherapy be listed specifically as a high-risk group and that they receive primary prophylactic treatment with G-CSF. Their suggestions are based on a number of different studies reporting not only the increased significance of neutropenic infections in the elderly, but the fact that they lead to a longer duration of hospitalisation, involving a substantial increase in the cost per infection.[61]

3. Approaches to Improving Chemotherapeutic Outcome

Attempts to improve the outcome of breast cancer chemotherapy have included searching for more effective agents, combinations of agents, and dosage regimens (timing and duration), optimising dosage, and finding prognostic markers for response to individual therapies. Promising new agents include the taxanes and new hormonal therapies. The addition of other chemotherapeutic agents to established regimens such as CMF has to date not reliably improved outcome.[7] The value of simultaneously combining hormonal therapy with cytotoxic chemotherapy remains unproved.

Another approach is very high-dose chemotherapy. Increasing the dosage to levels that completely ablate neutrophils requires haematopoietic support – typically reinfusion of stem cells derived from bone marrow or peripheral blood progenitor cells (PBPCs). Filgrastim is used adjunctively for haematopoietic support following transplantation of autologous or allogeneic leucocyte stem cells.[62,63] Mobilisation of cells with filgrastim significantly shortens the time required to obtain sufficient stem cell yields obtained from each harvest.[64-69] Bone marrow stem cells or PBPCs are infused as nonenriched cell populations or as cells enriched for precursor and mature neutrophils, based on expression of the CD34 granulocyte marker.[70] Adjunctive use of filgrastim in stem cell transplantation decreases the time required for neutrophil recovery in patients receiving transplanted cells.[71-73] Stem cell transplantation with

autologous or allogeneic donor leucocytes, however, is currently used principally within the context of clinical trials.[45] Work by Hohaus and colleagues[74] has shown that sequential high-dose chemotherapy with PBPC support can be safely administered to women with high-risk stage II/III breast cancer. Further therapy intensification, including addition of non–cross-resistant drugs or immunological approaches such as the use of antibodies against HER-2/neu, may eventually be possible for patients with stage III disease and hormone receptor-negative tumours.[75]

Dose intensity refers to treatment dosage and frequency of administration (e.g. milligrams of drug per square metre per week).[76] Theoretical considerations of cell kinetics suggest that increasing the chemotherapeutic dose should increase the proportion of cancer cells killed and the probability of eradicating the cancer.[77] The importance to outcome of achieving the planned conventional dose has been demonstrated many times. On the basis of these considerations, it was hypothesised that outcome could be improved by intensifying the dose short of the point at which stem cell transplantation or PBPC infusion was required. Dose intensification may be achieved by increasing the dose of chemotherapy, reducing the interval between cycles, or both.

Haematological toxicity is commonly encountered among patients on dose-intense regimens and is often the basis for reduced dosage or delayed administration of the next cycle of therapy. Either approach reduces dose intensity, providing reduction in treatment toxicity at the expense of therapeutic effect.[76]

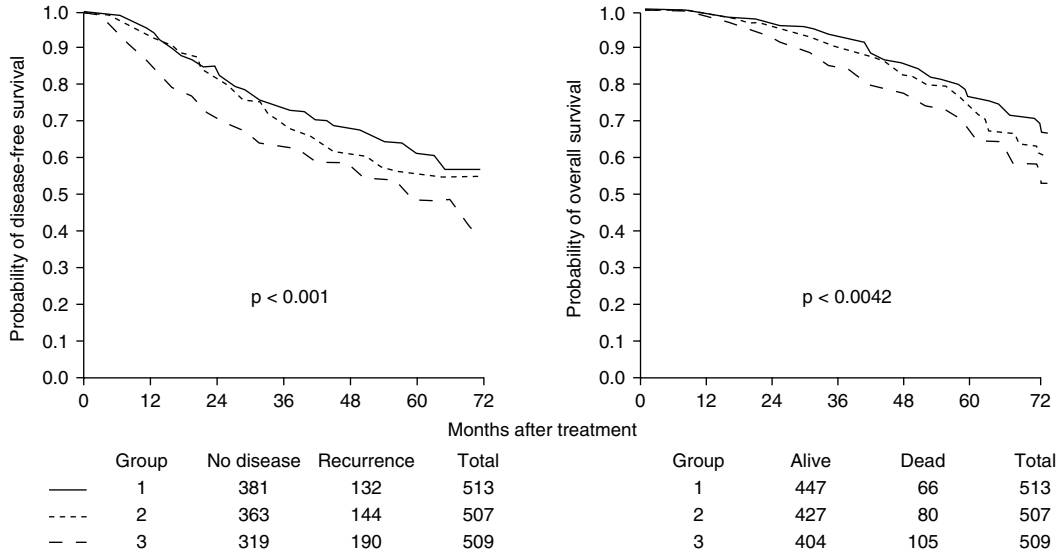
Several studies have reported promising results with high-dose–intensity chemotherapy; however, other reports have been conflicting, and most of these studies were uncontrolled.[62,78,79] The feasibility of reducing toxicity by adding filgrastim was demonstrated in a 5-year trial of intensified mitoxantrone 23 mg/m^2 plus cyclophosphamide 600 mg/m^2, with filgrastim.[39] Toxicity was generally mild, with no toxic deaths and a 3% incidence of FN.

High-dose–intensity therapy has been evaluated in a prospective, randomised trial among 1572 women with node-positive, stage II breast cancer.[80] Patients received one of three dose intensities of CAF: 75/7.5/150 mg/m^2/wk (low), 100/10/200 mg/m^2/wk (moderate) or 150/15/300 mg/m^2/wk (high). At 3-year follow-up, mean disease-free survival was 74, 70 and 63 months in the high-, moderate- and low-intensity groups, respectively. Disease-free survival was significantly longer in the moderate- and high-intensity groups than in the low-intensity group ($p < 0.001$). Overall survival was 92, 90 and 84 months, respectively. Overall survival was significantly longer in the moderate- and high-intensity groups than in the low-intensity group ($p = 0.004$). Survival plots showed the same significant differences between groups (figure 3). Toxicity increased with dose intensity. Grade III or IV leucopenia occurred in 65% of the high-intensity, 16% of the moderate-intensity, and <5% of the low-intensity group. The rates of thrombocytopenia were 18, <2% and <2%, respectively. However, in a randomised trial of over 2000 women with primary, operable breast cancer, doubling or quadrupling the intensity of cyclophosphamide in AC regimens had no effect on overall or disease-free survival.[81,82] Despite the use of adjuvant filgrastim, grade 4 neutropenia occurred in 20% of the women who received the standard regimen, 34% of those in the intensified group, and 49% of those who received the highest dose density.

The value of dose-intensive chemotherapy remains uncertain. Its evaluation must also take into account issues of cost, patient selection and life-threatening adverse effects. Newer high-dose treatment regimens may promote positive clinical outcomes with fewer associated adverse effects. [83]

4. Which Patients Should Receive Filgrastim?

The issue of cost has been extensively discussed in the literature as a potential barrier to the clinical use of filgrastim. Despite the well documented clinical benefits of filgrastim, its high cost has led



	Group	No disease	Recurrence	Total
——	1	381	132	513
- - - -	2	363	144	507
— —	3	319	190	509

Group	Alive	Dead	Total
1	447	66	513
2	427	80	507
3	404	105	509

Fig. 3. Disease-free and overall survival in women who received high-intensity (group 1), moderate-intensity (group 2) or low-intensity (group 3) CAF (cyclophosphamide, doxorubicin, fluorouracil) chemotherapy. *Probability of disease-free survival:* the numbers under the panel refer to the number of women in each treatment group who were free of disease or had recurrent disease at the time of the last analysis. *Probability of overall survival:* the numbers under the panel refer to the number of women in each treatment group who were alive or dead at the time of the last analysis. (Reproduced with permission from Wood W, Budman D, Korzun A, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994; 330: 1253-9.[80] Copyright© 1994 Massachusetts Medical Society. All rights reserved.)

to concerns about cost-effective approaches to its use. Current American Society of Clinical Oncology guidelines for use of colony-stimulating factors recommend prophylactic administration when the expected incidence of FN is ≥40% in previously untreated patients, when FN has occurred during a previous cycle of chemotherapy, for mobilisation of PBPCs prior to collection following myeloablative chemotherapy with autologous cell infusion, or in patients about to receive relatively nonmyelosuppressive chemotherapy but who have risk factors for FN because of compromised bone marrow or comorbidities (e.g. the elderly).[84,85] Furthermore, cost savings can be achieved at significantly lower thresholds of FN than has been previously thought. As noted in recent work by Lyman et al.,[86] the risk threshold for cost savings with filgrastim use during chemotherapy decreases by half (from 40 to 20%) when patients require lengthy hospitalisation for FN.

Clinical prediction models have been developed with certain tumours to permit rational selection of patients for filgrastim support. Patient records were analysed to determine correlations between pretreatment predictors of neutropenia (e.g. pretreatment history and therapy regimen) and conditional predictors, such as first-cycle nadir of ANC and serum haemoglobin levels.[52,87,88] The model was validated in another population of 80 patients. This model concluded that it is possible to rank patients according to their risk of subsequent neutropenic complications (and, therefore, their relative need for supportive treatment with filgrastim) predominantly on the basis of their ANC during the first cycle of chemotherapy. Providing filgrastim to the neediest 50% of early-stage breast cancer patients (as defined by first-cycle blood counts), beginning after the first cycle of chemotherapy, was associated with a calculated cost-effectiveness ratio of $US34 297 per life-year saved (figure

4).[52] This value is well within the range of accepted cost-effectiveness ratios for the treatment of other common medical conditions. Current guidelines for the cost-effective use of filgrastim should, therefore, be re-evaluated in the light of available information on the total cost of FN and the cost effectiveness of filgrastim in specific clinical situations.[52,86,89]

Use of the ANC at the nadir of the first cycle of chemotherapy to predict subsequent toxicity was validated in subsequent studies. Among 143 patients with stage I, II or IIIa breast cancer, first-cycle ANC nadir was the only significant predictor of neutropenic events in subsequent cycles ($p < 0.0001$).[88] Patients with a first-cycle ANC nadir <250/μl experienced a significantly higher number of episodes of FN (30 *vs* 10%, $p = 0.04$) and were significantly more likely to receive <85% of the planned dose intensity (55 *vs* 32%, $p = 0.05$). Estimated relative risk of a neutropenic event for patients with a first-cycle ANC nadir <500/μl was 4.8, which was similar to the prediction of the Silber model (4.4).[87] In a prospective validation study of the Silber model, 624 patients with stage I-III breast cancer receiving adjuvant AC, CAF or CMF were stratified by depth of first-cycle ANC nadir.[90] High-risk patients were given prophylactic filgrastim for subsequent cycles. Low-risk patients were treated with filgrastim only after experiencing a febrile neutropenic event or delayed haematological recovery from a previous chemotherapy cycle. The percentage of patients receiving 85% of the planned dose intensity and the percentage hospitalised for FN were compared with matched historical controls. By implementing the model, the percentage of patients who received <85% of the planned dose scheduled, the percentage of patients who experienced an episode of FN, and the percentage of patients who required hospitalisation for FN were significantly lower than for controls (all $p < 0.05$).

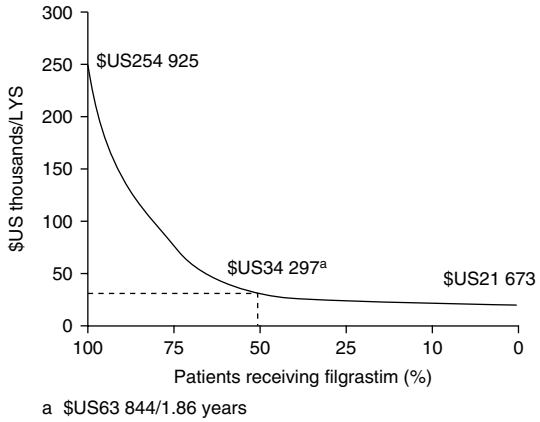


Fig. 4. Cost-effective use of granulocyte colony-stimulating factor in breast cancer: threshold relationship to marginal cost-effectiveness ratios. Cost-effective use of filgrastim in early-stage breast cancer: the association between the percentage of patients receiving filgrastim and the mean incremental cost per life-year saved (LYS). If all patients were treated with filgrastim after the first cycle, the average cost-effectiveness ratio would be $US254 925/LYS. If all patients first must develop an event before filgrastim use, the mean increment would be $US21 673/LYS. If filgrastim were given to the 50% of patients at greatest risk, the mean increment would be $US34 297/LYS. (Based on age at diagnosis of 55 years.) [Reproduced from Lyman GH,[52] with permission.]

5. Future Directions

Several lines of evidence suggest that filgrastim may prove to be useful in combination with immunological therapies (e.g. monoclonal antibodies).

Other cellular adhesion receptor-ligand pairs, such as CD49d (VLA-4)/laminin or CD49d/vitronectin, appear to work in conjunction with filgrastim to promote mobilisation of myeloid precursors from bone marrow into the peripheral circulation. *Ex vivo* culture of PBPCs in a growth factor cocktail, followed by expansion in filgrastim alone, yields high numbers of mature neutrophils fully competent for microbial killing and chemotaxis.[91,92] Killing of microbes and tumour cells is enhanced by specific serum antibodies, and filgrastim may increase the cytotoxic capacity of neutrophils by virtue of sustained or increased levels of antibody-binding receptors (CD64, FcγRI) on cell surfaces.[93-95] Increased binding of neutrophils to tumour or microbial target cells promotes phagocytosis of the target cells.[96] Filgrastim enhances the killing capacity of neutrophils through activation of a respiratory oxidative burst that is

associated with intracellular destruction of engulfed cells or microbes.[97,98] Additionally, filgrastim does not significantly inhibit resident (CD8+) T-cell– or natural killer (NK)-cell–mediated cytotoxicity,[99-101] and therefore may be used to expand autologous stem cells without decreasing the endogenous lytic function of resident NK cells or tumour-specific immune T cells.

An interesting immunological feature of filgrastim is its ability to down-regulate cellular expression of pro-inflammatory cytokines by lymphocytes.[102,103] This phenomenon, noted both *in vivo* and *in vitro*, may reduce or slow the deleterious graft-versus-host disease (GVHD) that often accompanies allogeneic stem cell transplantation. Conversely, this potentially beneficial effect on GVHD may eliminate the so-called 'graft-versus-tumour' effect observed with allogeneic cell transfers that is considered to be important for successful elimination of tumour cells *in vivo*.[104]

Recent advances in the therapeutic use of monoclonal antibodies against tumour cells have rekindled interest in cancer immunotherapy. For example, immunotherapeutic approaches using bispecific antibodies to direct immune effector cells toward target tumour cells have been shown to be effective in a number of studies.[96,105-108] These antibodies can potentially eliminate the micrometastases that may persist in tissues after breast cancer chemotherapy, by virtue of amplified recognition and lysis by neutrophils and other immune effector cells. This process of tumour cell destruction is mediated through FcγRI [CD64, high-affinity receptor for immunoglobulin (Ig) G] expressed on activated neutrophils and monocytes[94,109] or FcαRI (CD89, IgA receptor).[110] Recent studies have shown that filgrastim and granulocyte-macrophage colony-stimulating factor can increase the number and per-cell cytotoxic capacities of FcγRI-positive neutrophils and monocytes.[93,95,110] Bispecific antibodies may also work well in conjunction with chemotherapeutic agents in eliminating breast cancer cells,[16] thus defining a new therapeutic area of investigation for these reagents.

Another potential therapeutic application for bispecific antibodies is described by Maletz et al.,[111] who used antibodies recognising the HER2 (c-erbB2) receptor and the T-cell–receptor component CD3 to cytolytically purge breast cancer tumour cells from human stem cell preparations. The efficiency of tumour cell depletion methods can be measured immunocytochemically or by polymerase chain amplification of tumour cell-specific primers.[112,113]

The addition of other cytokines may eventually be used to enhance filgrastim-stimulated mobilisation of immune effector cells into stem cell grafts. Sosman and co-workers[114] recently explored this possibility by administering interleukin-2 (IL-2) plus filgrastim to 32 women with advanced breast cancer undergoing high-dose chemotherapy and autografting. Immune reconstitution was superior in patients mobilised with IL-2 plus filgrastim, based on increased numbers of activated T cells, activated NK cells and enhanced lymphokine-activated killer-cell activity. The authors concluded that filgrastim plus IL-2 enhances the number and function of antitumour effector cells in mobilised autografts without impairing haematological engraftment, provided that CD34+ cell counts are higher than 1.5×10^6 cells/kg. In a similar study, Burns and colleagues[115] showed that the addition of IL-2 to filgrastim-stimulated peripheral cell mobilisation promoted cytotoxicity of IL-2–activated mononuclear cells from the PBPC product against the breast cancer target cells and increased the percentage of NK cells and activated T cells in the leukapheresis product. Immunisation may also find a place in the breast cancer treatment armamentarium. Gene therapy may offer a useful avenue for future clinical treatments related to filgrastim. In a recent trial by Yin and colleagues,[116] retroviral-based introduction of genes imparted chemotherapy sensitisation to tumour cells and resistance to normal cells. Results of the same study suggest that chemotherapy administered after gene therapy generates more favourable therapeutic responses than does a single exposure to intensive systemic chemotherapy.

Current clinical practice guidelines for the use of filgrastim in women with breast cancer are likely to be re-evaluated in the light of recent cost-effectiveness findings and the development of accurate prognostic risk factor models.[52] Clinical decision-makers should look beyond simple cost-minimisation strategies to evaluate the effects of available treatments on patient survival and quality of life.[117] With this in mind, plus the overall immunological benefits achieved with adjuvant growth factors (e.g. reconstitution of endogenous or transplanted immune functions), the use of filgrastim may be considered for any patient receiving chemotherapy for a potentially curable malignancy, such as early-stage breast cancer, when it is required to maintain haematopoietic stasis during myelosuppressive chemotherapy.[52]

A pegylated form of filgrastim has recently been developed and was tested in phase III randomised, double-blind clinical trials with breast cancer patients. This sustained-duration form of filgrastim (pegfilgrastim) was administered to patients once per cycle of doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) for four total cycles of chemotherapy. Data from two independent studies indicated that pegfilgrastim was as effective as daily filgrastim injections in reducing the duration of severe neutropenia and FN. Pegfilgrastim can potentially simplify treatment of neutropenia and increase adherence to chemotherapy regimens in cancer patients.[53,118]

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