Use of G-CSF to Sustain Dose Intensity in Breast Cancer Patients Receiving Adjuvant Chemotherapy : A Pilot Study

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Breast Cancer patients receiving adjuvant chemotherapy can safely continue on full-dose intensity therapy using supportive treatment with recombinant G-CSF.

Background: Adjuvant chemotherapy for breast cancer is frequently accompanied by neutropenia requiring dose reduction or treatment delay that can potentially compromise therapeutic effectiveness. Recombinant granulocyte-colony stimulating factor (G-CSF) reduces the duration and severity of neutropenia.

Methods: Nineteen patients with newly diagnosed breast cancer receiving adjuvant systemic chemotherapy met criteria for dose reduction or treatment delay due to neutropenia. All were treated with G-CSF. The mean duration of G-CSF therapy was five days.

Results: An increase in mean absolute neutrophil count was seen in cycles with G-CSF. Chemotherapy treatment was delayed less often following the use of G-CSF.

Conclusions: Breast cancer patients receiving adjuvant chemotherapy who face treatment delays or dose reductions can continue on full-dose intensity therapy using supportive G-CSF. Prospective trials are needed to accurately measure the impact of G-CSF on dose intensity and long-term disease control.

Introduction

Adjunctive systemic chemotherapy has been shown to reduce the risk of recurrence and improve disease-free and overall survival in women with early-stage breast cancer.[1] The efficacy of treatment on survival is assumed to be directly related to the administered dose intensity.[2,3] The major dose-limiting toxicities associated with systemic chemotherapy are myelosuppression and associated neutropenia.[4,5] The onset of fever in the setting of neutropenia (FN) necessitates hospitalization for empiric, broad-spectrum parenteral antibiotics. Treatment-related neutropenia may necessitate either a reduction in chemotherapy dose or a delay in treatment, thus resulting in decreased dose intensity. A reduction in the intensity of chemotherapy dose may result in increased risk of disease recurrence and eventual disease-related mortality. Human recombinant granulocyte colony-stimulating factor (G-CSF) has been shown to attenuate the severity and duration of neutropenia associated with systemic chemotherapy.[4,6-10] Human recombinant G-CSF therapy is generally used to reduce the risk of infection in patients at high risk for FN based on the intensity of treatment, the prior occurrence of FN, or the presence of other risk factors for infectious complications.[4,5,11,12]

This pilot study is based on the rationale that relatively short courses of G-CSF may reduce the need for a reduction in chemotherapy dose or a delay in treatment for patients at risk for FN, thus permitting administration of full-dose intensity systemic chemotherapy. This study assesses the feasibility of future prospective trials to evaluate the ability of G-CSF to sustain dose intensity in breast cancer patients who are receiving adjuvant chemotherapy. Sustaining dose intensity by decreasing the need for dose reduction or treatment delay may reduce the risk of disease recurrence and may improve overall survival.

Methods

Women receiving adjuvant systemic chemotherapy were identified who met criteria for dose reduction or treatment delay based on the severity or duration of neutropenia. After written informed consent, patients were offered continued full-dose intensity adjuvant chemotherapy concurrent with a course of human G-CSF at a dose of 5 μg/kg daily administered subcutaneously in a nonrandomized fashion. Most patients received short courses (five days) of G-CSF beginning seven to 10 days following chemotherapy. Differences in physician practice and treatment dates resulted in some variation in the interval to the initiation of G-CSF. Patients were generally treated in a uniform fashion over subsequent cycles. The following parameters were monitored in patients before and after the initiation of G-CSF using patients as their own controls: (1) hemoglobin concentration, white blood cell count, absolute neutrophil count (ANC), and platelet count, (2) other treatment-related toxicities including mucositis, nausea and vomiting, and diarrhea, (3) incidence of FN and hospitalization, (4) magnitude of any dose reduction, (5) duration of any treatment delay, and (6) overall dose intensity of chemotherapy.

Treating physicians were asked to follow their individual practices regarding modifications in chemotherapy dose or delays in treatment. Therefore, dose reductions and treatment delays were evaluated under the conditions of actual practice. Dose reductions and treatment delays were also evaluated using a standard set of criteria. The criterion used for dose reduction was either a prior episode of FN or a nadir ANC of less than 500 cells/µL. The standard criterion for treatment delay was a recovered ANC of 1,500 cells/µL or less at the next scheduled treatment. Intensity of chemotherapy dose was defined as the dose delivered per unit of time. Measured outcomes before and after the initiation of G-CSF were compared on the basis of either a paired sample t test or Wilcoxon Signed Rank test. Categorical outcomes before and after initiation of G-CSF were compared using either exact methods or a chi-square test applied to untied observations.
**Results**

Nineteen patients receiving adjunctive systemic chemotherapy for early-stage breast cancer were entered on this study. All patients met practice criteria for dose reduction or treatment delay due to current or previous neutropenia. All patients were white women with a median age of 47 years (Table 1). The stage of disease included six stage I, eight stage IIA, four stage IIB, and one stage IIIA. Of the 19 patients, 12 (63%) underwent lumpectomy and seven (37%) underwent a modified radical mastectomy. Radiation therapy was administered in 14 patients (74%), including 11 (58%) who received this treatment either prior to or concurrent with chemotherapy. Two patients (11%) received hormonal therapy either prior to or concurrent with chemotherapy. Thirteen patients (68%) received cyclophosphamide, methotrexate, and fluorouracil (CMF), and six (32%) received either cyclophosphamide and doxorubicin (CA) or CA with fluorouracil (CAF) adjuvant therapy (Table 2). Chemotherapy was intravenously administered on three-week cycles. Patients received 63 cycles (median: 3 per patient; range: 1-5) prior to initiating G-CSF and 44 cycles (median: 3 per patient; range: 1-5) subsequent to beginning G-CSF. The median and mean times to initiation of G-CSF (± standard error of the mean) were 8 and 8.3 (± 0.9) days, respectively. The median and mean duration times of G-CSF treatment (± standard error of the mean) were 5 and 6.4 (± 0.5) days, respectively. The mean ANC prior to and following the initiation of G-CSF is shown in Fig 1. Differences in the mean ANC reveal a significant effect while on G-CSF for each week of the cycle (Table 3).

Prior to initiating G-CSF, all patients met the criteria for dose reduction or treatment delay. Following the onset of G-CSF, doses were reduced in only three patients (16%), and treatment was delayed in six patients (31%). A significant difference in the proportion of patients experiencing treatment delays was observed (P<.05), while no significant difference in the proportion undergoing dose reduction was found. Dose reduction was attributed to prior neutropenia in one patient and to undocumented reasons in two patients. Treatment delay was attributed to either prior febrile neutropenia or persistent neutropenia in four patients and to compliance or scheduling problems in two patients. The proportion of cycles associated with dose reduction or treatment delay before and after the initiation of G-CSF are shown in Fig 2. Dose intensity following the initiation of G-CSF was greater than dose intensity prior to initiation (Fig 3). Differences in intensity were small, however, and reached statistical significance only for cyclophosphamide (P=.048). Differences in dose intensity are attributable to fewer dose reductions or treatment delays after the initiation of G-CSF and, in some cases, a return to the originally targeted doses. Standard criteria for treatment delay based on an ANC of 1,500 cells/µL or less at the start of each cycle were met in 18 patients (95%) prior to the initiation of G-CSF and in only six patients (32%) following the start of G-CSF (P<.001). Based on FN or an ANC of 500 cells/µL or less at any time during the preceding cycle, the criteria for dose reduction were met in eight patients (42%) prior to the initiation of G-CSF and in only three patients (16%) following the start of G-CSF (not significant). There was no significant change in the incidence of FN or other toxicities following initiation of G-CSF.
Discussion

After the initiation of G-CSF, the following effects were observed: (1) cycles of chemotherapy were associated with significantly higher ANC, (2) the proportion of cycles associated with treatment delay was significantly reduced, (3) fewer patients met standard criteria for dose reduction or treatment delay, (4) the proportion of the targeted dose actually administered for each drug did not decrease further, and (5) no overall decrease in dose intensity or increase in incidence of FN was shown. The results of this pilot study suggest that breast cancer patients receiving standard adjuvant chemotherapy who meet criteria for dose reduction or treatment delay can safely continue on full-dose intensity chemotherapy using relatively short courses of G-CSF. A small increase in dose intensity was actually observed as physicians were sometimes able to resume targeted dose and schedule after the initiation of G-CSF.

Our study has several limitations. The criteria for treatment delay and dose reduction used by physicians were not uniform among the treating clinicians. Therefore, results based on a hypothetical set of standard guidelines were presented. Also, the study population of only 19 patients provides a low power to detect small differences in treatment measures.

Hematopoietic growth factors have demonstrated value in the management of patients receiving systemic cancer chemotherapy. Nevertheless, these agents are costly and have not yet shown substantial improvement in survival in this setting. Guidelines have been developed for the use of these agents based largely on considerations of cost-effectiveness.[4,5] Studies of the therapeutic use of G-CSF only after the onset of FN have produced conflicting results.[8,9] Human G-CSF has been shown to reduce the duration and severity of neutropenia and the incidence of FN when used prophylactically between cycles of systemic chemotherapy.[6] Patients at high risk for FN in this setting include those receiving intensive chemotherapy regimens, those with a prior episode of FN on the same regimen, and those with comorbid conditions that in-crease the risk associated with FN. The value of these agents in patients with potentially curable malignancies who receive less intensive regimens has not been studied adequately. The importance of sustaining dose in-tensity in such patients is generally acknowledged despite practice standards that require dose reduction or treatment delay in many patients.

Conclusions

This study demonstrates that patients with breast cancer who receive adjuvant chemotherapy and who face treatment delays or dose reductions can continue full-dose intensity therapy by administering supportive treatment of G-CSF. A small increase in dose intensity was actually observed as physicians were sometimes able to resume targeted dose and schedule after the initiation of G-CSF.

References


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