A Retrospective Analysis of the Effect of Ethnic Neutropenia on Reduced Chemotherapy Dose Intensity in African-American Women with Early Stage Breast Cancer

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A. Study Purpose and Rationale

Adjuvant chemotherapy is administered to women with early stage breast cancer (stages I-III) to prevent cancer recurrence after tumor resection and radiation therapy. With current chemotherapy regimens overall and disease-free survival can by improved by 23.5% and 14.3%, respectively[1]. It has been observed that African-American women with breast cancer have a worse prognosis compared to Caucasian women. The mortality rate for breast cancer is 35.8 per 100,000 African-American women compared to 23.6 Caucasian women[2, 7]. This difference persists even after correction for known prognostic factors such as age, stage at presentation, and tumor biology. One possible explanation for this increased mortality rate is that African-American women are inadequately treated. African-American women receive similar benefits from chemotherapy compared to Caucasian women. However, studies have shown that African-American women receive less optimal chemotherapy regimens[1, 3]. The reasons for this difference are not clear.

Chemotherapy regimens for breast cancer are dosed based on actual body weight and standardized regimens which produce superior survival outcomes have been determined. Several large studies have demonstrated that the benefits of chemotherapy are diminished or even lost when doses are either reduced or delayed[4]. An entity called relative dose intensity (RDI) incorporates both the total dose delivered and the duration of treatment compared to standard regimens. RDI less than 85% has been associated with poorer survival[4]. For this reason it is especially concerning that African-American women on average receive a lower RDI. Potential confounders in this association such as obesity and socioeconomic status have been investigated and are not sufficient to explain these differences[1].

Deviations from the standard chemotherapy regimen can occur in two ways. The dose may be reduced beginning with the first cycle if the oncologist anticipates that the patient will not be able to tolerate the adverse effects of the full dose. This occurs in 10-20% of patients[5]. Alternatively, subsequent chemotherapy doses may be reduced or delayed in response to these side effects. The most common dose-limiting effects of adjuvant chemotherapy for breast cancer are nausea/vomiting and neutropenia. Dose reductions or delays are common: a national survey of community oncology practices found that 55.5% of patients received an RDI of less than 85%[1]. Factors associated with a greater incidence of neutropenia and reduced RDI include chemotherapy regimen used (doxorubicin vs. cyclophosphamide and dosing schedule), age, performance status, and use of colony stimulating factors[6].

African-American women on average have lower baseline white blood cell counts than Caucasian women[2]. This difference has been termed "ethnic neutropenia." It suggests a possible explanation for the observed reductions in chemotherapy administered to African-American women. It is possible that women with lower pretreatment WBC counts are more likely to become neutropenic during the course of therapy necessitating dose reductions or delays. Additionally, it is possible that when treating patients with low baseline WBC counts, oncologists reduce the planned dose of chemotherapy in anticipation of neutropenia. The aim of this study is to determine whether differences in baseline WBC count could contribute to the observed differences in chemotherapy administered to Caucasian and African-American women.

B. Study Design and Statistical Analysis

The study will be a retrospective analysis of all women treated for stage I-III breast cancer at CPMC between 1999 and 2004 who are 18 years of age and older, designated African-American or White Non-Hispanic, and treated with an anthracycline-based chemotherapy regimen. In order to differentiate between dosing changes made in response to neutropenia and those made in anticipation of neutropenia, women who have planned dose reductions as determined by a first dose of less than 90% of the standard dose will be excluded from the primary analysis. The primary outcome will be the relative dose intensity (RDI) of chemotherapy delivered. A secondary outcome will be the dose proportion administered in the first cycle. A further analysis of interest will include the relationship between WBC nadir and the primary outcome.

The database contains 202 Caucasian subjects and 135 African-American subjects who fulfill the above criteria. A single variable correlation test will be run separately within the two racial groups to evaluate the association between initial WBC count and RDI. A patient population of this size is sufficient to detect any clinically significant association (correlation coefficient > 0.24) with a power of 80% and an alpha of 0.05. Logistic regression analyses will be performed to account for possible confounding due to other variables known to be associated with reduced RDI such as age, performance status, and use of colony-stimulating factors.

C. Study Procedure

No procedures are included in this study.

D. Study Drugs

No drugs are administered for the purposes of this study.

E. Medical Device

No medical devices are used in this study.

F. Study Questionnaires

No questionnaires are necessary for this study.

G. Study Subjects

The subjects are part of a database of women treated for stage I-III breast cancer at CPMC between 1999 and 2004. Subjects must be identified as African-American or White, Non-Hispanic and have received a doxorubicin-containing chemotherapy regimen. Women who receive less than 90% of the standard on the first dose will be excluded. Women included in this database previously signed consent for information to be used in future research studies. The study is restricted by gender and race in order to explore previously described differences in treatment and outcomes.

H. Recruitment of Subjects

No recruitment is necessary for this study.

I. Confidentiality of Study Data

All data in the patient database is coded. Data will be stored in a secure location accessible only to investigators.

J. Potential Conflict of Interest

There is no potential conflict of interest.

K. Location of the Study

The study will take place only within CPMC.

L. Potential Risks

There are no potential risks.

M. Potential Benefits

Understanding the reasons for inadequate chemotherapy delivery to African-American women may enable clinicians to alter this pattern and improve survival rates among African-American women with breast cancer. Furthermore, this study may identify baseline WBC count as a risk factor for chemotherapy-induced neutropenia and reduced dose intensity. This information could be useful in creating a prediction model to determine which patients would most likely benefit from colony stimulating factor prophylaxis.

N. Alternative Therapies

NA

O. Compensation to Subjects

None.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

No minors will be included in this study

R. Radiation or Radioactive Substances

No radioactive substances are involved in this study.

S. References:

1. Lyman GH, Dale DC, Crawford J. Incidence and Predictors of Low Dose-Intensity in Adjuvant Breast Cancer Chemotherapy: A Nationwide Study of Community Practices. J Clin Oncol 2003;21:4524-4531.

2. Griggs JJ. Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. Breast Cancer Research and Treatment 2003;81:21-

3. Hershman D, Weinberg M, Rosner Z, Alexis K, Tiersten A, Grann V, Troxel A, Neugut A. Ethnic Neutropenia and Treatment Delay in African-American Women Undergoing Chemotherapy for Early Stage Breast Cancer. J Natl Cancer Inst 2003;95:1545-1548.

4. Citron ML. Dose Density in Adjuvant Chemotherapy for Breast Cancer. Cancer Investigation 2004;22:555-568.

5. Griggs JJ, Sorbero MES, Lyman GH. Undertreatment of Obese Women Receivving Breast Cancer Chemotherapy. JAMA 2005;165: 1267-1273.

6. Lyman GH, Lyman CH, Agboola O. Risk Models for Predicting Chemotherapy-Induced Neutropenia. The Oncologist 2005;10:427-437.

7. Newman LA, Mason J, Cote D, Vin Y, Carolin K, Bouwman D, Colditz GA. African-American ethnicity, socioeconomic status, and breast cancer survival: A meta-analysis of 14 studies involving over 10,000 African-American and 40,000White American patients with carcinoma of the breast. Cancer 2002;94: 2844-2854.