

# Dose Intensity in Early-Stage Breast Cancer: A Community Practice Experience

By Robert L. Bretzel Jr, RPh, Ralph Cameron, PharmD, Marc Gustas, PharmD, Maria A. Garcia, RN, OCN, Heather K. Hoffman, RN, OCN, Rosalind Malhotra, RN, BSN, OCN, Karen Miller, RN, BSN, OCN, Janine Prime, RN, BSN, OCN, and Anne Favret, MD

Fairfax Northern Virginia Hematology Oncology, Fairfax, VA

## Abstract

**Purpose:** This retrospective study was a quality initiative to determine practice patterns in adjuvant chemotherapy for early-stage breast cancer (ESBC) and define the incidence and causative factors of suboptimal relative dose intensity (RDI). Our community-based practice participates in ASCO's Quality Oncology Practice Initiative in an effort to improve the quality of care provided to our patients. Most metrics do not have a direct proven correlation with improvement in survival, but measurement of RDI does.

**Patients and Methods:** Our study was a retrospective analysis of patients with ESBC. Each patient was treated on an outpatient basis in a community practice setting. We used the diagnosis criteria of breast cancer to create a list of eligible patients within the data range from our electronic medical record.

Inclusion criteria consisted of all women seen in our offices receiving adjuvant chemotherapy for a diagnosis of breast cancer. Exclusion criteria included patients with metastatic disease and patients not receiving chemotherapy.

**Results:** The average weighted RDI for all patients was 98.4%. Of the 834 evaluable patients we reviewed, 102 patients (12.2%) had some reduction in RDI. This subset had an average RDI of 88%. Twenty-nine patients (3.5%) had an RDI of less than 85%.

**Conclusion:** Because decreased RDI has been shown to correlate with decreased overall and disease-free survival rates, we were compelled to measure and determine causative factors in our patients with ESBC. The primary reasons for dose delay and overall reduction in RDI were scheduling and neutropenia. Scheduling delays were initiated by both patients and medical staff, with the majority requested by patients.

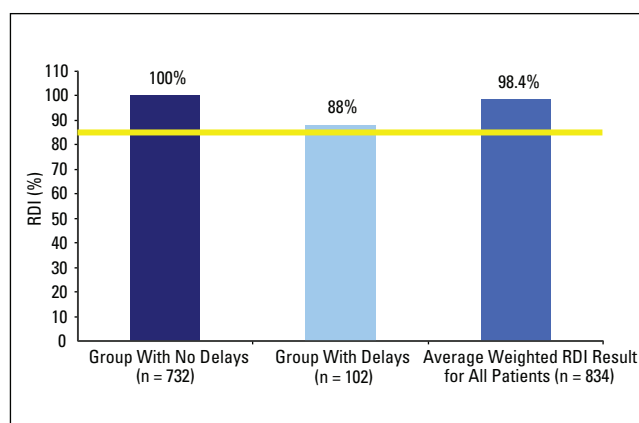
## Introduction

Breast cancer remains a common and often highly treatable malignancy. Early-stage breast cancer (ESBC) comprises 91% of all breast cancer cases diagnosed each year, and most patients are treated in the adjuvant setting with curative intent.<sup>1</sup> Although the intrinsic properties of breast cancer, such as nodal status, grade, size, and receptor status, play roles in determining prognosis, there is increasing evidence that maintaining dose intensity for breast cancer increases the disease-free survival (DFS) rate and affects the overall survival (OS) rate.<sup>2-4</sup> Relative dose intensity (RDI) is the relationship of the actual dose and schedule of chemotherapy delivered to the intended dose and schedule of the standard chemotherapy regimen. Decreases in RDI can be results of dose delays (DDs) and dose reductions (DRs). Using a practice-wide electronic medical record (EMR) system, we retrospectively evaluated our experience with 834 patients in a large community practice setting.

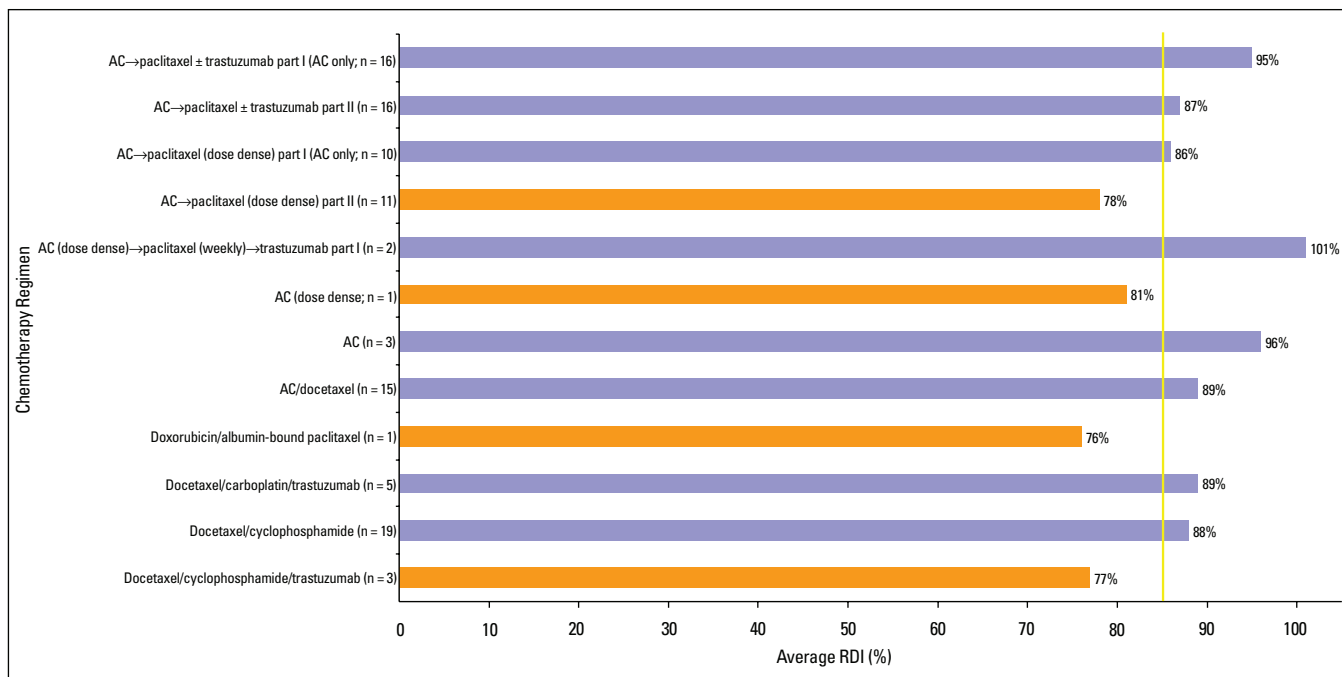
Although controversial, the relationship between dose intensity of chemotherapy and patient outcomes is well described in the literature.<sup>2-14</sup> Several studies discuss the significance of achieving an RDI of more than 85%.<sup>3-4,10,11</sup> Evidence continues to confirm that maintaining dose intensity for certain cancer types increases DFS and OS rates.<sup>2-4</sup>

The population of patients with ESBC has been studied in relation to RDI because of curative intent and effects on DFS and OS. In the 30-year follow-up to the landmark Bonadonna et al<sup>4</sup> study, among patients with ESBC treated with cyclophosphamide, methotrexate, and fluorouracil, relapse-free survival and OS rates were highest in those who received a dose intensity of at least 85%. Several studies have shown that despite these data, many patients

with ESBC continue to receive reduced RDI.<sup>3-8,11,14</sup> Results of a retrospective nationwide survey of approximately 11,000 patients revealed that more than half of patients with ESBC received an RDI of less than 85%.<sup>5</sup> DRs and/or DDs can easily result in an overall RDI of less than 85%. For example, a collective delay in treatment of more than 2 weeks or a DR of 20% will result in an RDI of 80%. Bonadonna et al<sup>3,4</sup> demonstrated that patients receiving an RDI of less than 85% experienced outcomes similar to those experienced by the control group. Chirivella et al<sup>2</sup> demonstrated that an RDI of less than 95% was associated with decreased OS in patients with ESBC treated with anthracycline, nontaxane-based chemotherapy.



**Figure 1.** Relative dose intensity (RDI) received by patients studied. Yellow line represents optimal RDI of at least 85%.



**Figure 2.** Average relative dose intensity (RDI) by chemotherapy regimen. Yellow line represents optimal RDI of at least 85%. Orange bars indicate the four regimens in which RDI < 85% was demonstrated. AC, doxorubicin/cyclophosphamide.

### Patients and Methods

Our study was a retrospective analysis of patients with ESBC. Each patient was treated on an outpatient basis in a community practice setting. We used the diagnosis criteria of breast cancer to create a list of eligible patients within the data range from iKnowMed, our EMR system. Inclusion criteria consisted of all women seen in our offices receiving adjuvant chemotherapy for a diagnosis of breast cancer between September 1, 2007, and August 31, 2008. The decision regarding the advisability of chemotherapy was made at the discretion of the attending physician. Exclusion criteria included patients with metastatic disease and patients not receiving chemotherapy.

The total number of evaluable patients was 834. Of these patients treated within the data range, we used our EMR to determine which subset of these patients experienced DDs and/or DRs during adjuvant chemotherapy treatment by reviewing individual medical records. All data were obtained through our EMR. We also identified and quantified the reasons for DDs and DRs. The data from the subset of patients with reduced DDs and DRs were then entered into an RDI calculator (RDI Calculator Specification, Version 2; NearSpace, Rohnert Park, CA; Data Supplement, online only).

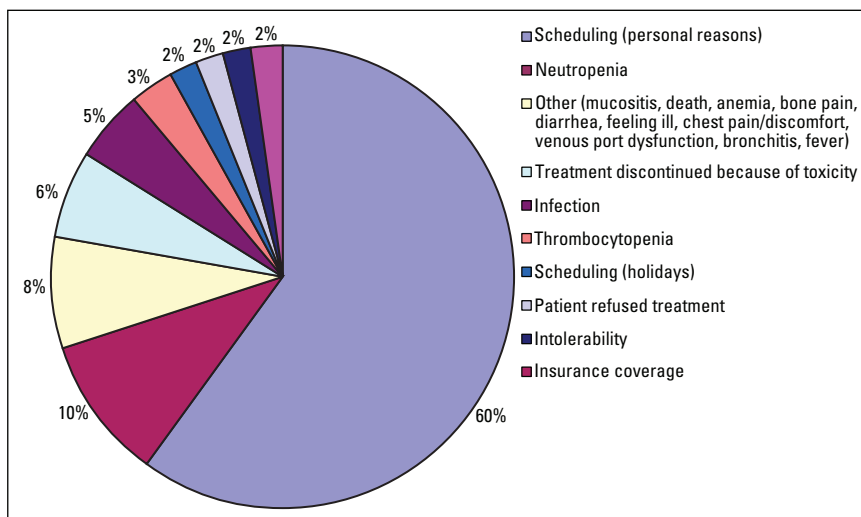
Within the subset, the following parameters were measured via the RDI calculator: average RDI total, average RDI by treating physician, average RDI by treating institution, average RDI by cancer stage, average RDI by treatment regimen, average RDI by age

group, and average RDI by patient risk factors (cardiovascular disease, liver disease, and diabetes mellitus). For those patients who experienced neutropenia as a cause of DD or DR, use or omission of colony-stimulating factors (CSFs) was noted.

### Results

The average weighted RDI for all patients was 98.4% (Fig 1). Of the 834 evaluable patients we reviewed, 102 patients (12.2%) had some reduction in RDI. This subset had an average RDI of 88%. Twenty-nine patients (3.5%) had an RDI of less than 85%.

For the purpose of this study, we focused on the subset group that showed a reduction in RDI. This group comprised patients



**Figure 3.** Causes of delayed chemotherapy by percentage of events.

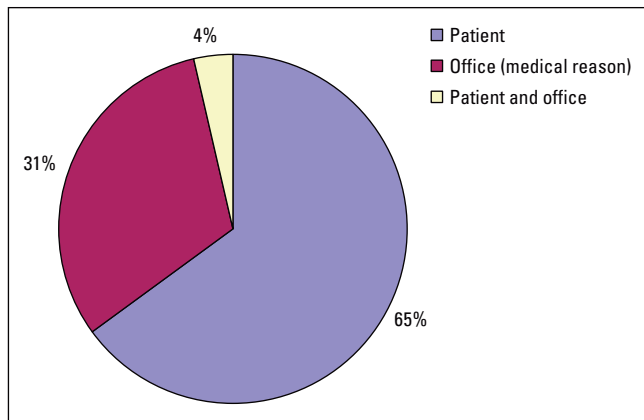


Figure 4. Reasons for scheduling delays.

with stage I (23%), stage II (51%), and stage III (26%) ESBC. Average RDI by staging was as follows: stage I (88%), stage II (88%), and stage III (86%). We reviewed data from eight treatment sites within our practice to determine trends by site. We also quantified the average RDI in this subset by physician to determine trends.

Average RDI by regimen administered was calculated. Of note, four (33%) of 12 regimens demonstrated an average RDI of less than 85% in this subset. They were: dose-dense doxorubicin/cyclophosphamide (AC) followed by paclitaxel (paclitaxel portion); dose-dense AC; doxorubicin/nanoparticle albumin-bound paclitaxel (Abraxane; Abraxis BioScience, Los Angeles, CA); and doxorubicin/cyclophosphamide/trastuzumab (Herceptin; Genentech, South San Francisco, CA; Fig 2).

The most common reasons noted for DDs were scheduling (both patient and medical reasons), neutropenia, treatment toxicity, infection, and other (Fig 3). The majority (65%) of scheduling delays were because of patient rather than office decisions (Fig 4).

We also studied the causes of delays as a result of risk factors. Most patients (60%) had no risk factors other than being fe-

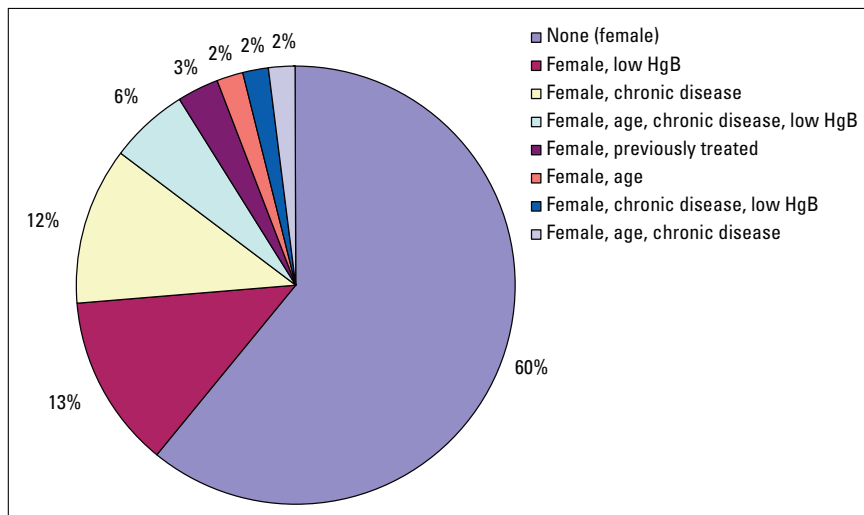


Figure 5. Delays as a result of risk factors. HgB, hemoglobin.

male. Chronic disease (comorbidities such as cardiovascular disease, liver disease, and diabetes mellitus) and low hemoglobin levels were also noted as causes of DDs (Fig 5).

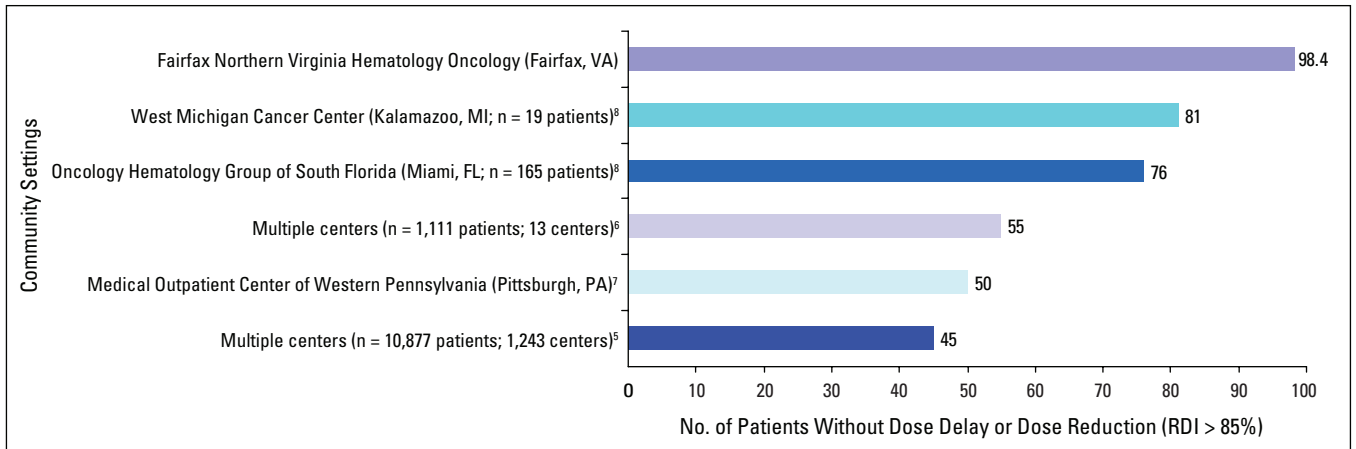
### Discussion

Before this initiative, RDI was not routinely calculated for our patients with ESBC. However, because decreased RDI has been shown to correlate with decreased OS and DFS rates, we were compelled to measure and determine the causative factors. The primary reasons we observed for DDs and overall reduction in RDI were scheduling and neutropenia. Scheduling delays were initiated by both patients and medical staff, with the majority requested by patients.

We observed that neutropenia often resulted in DDs, especially in patients who did not receive primary prophylaxis with CSFs. This trend follows other published data.<sup>5-7,9</sup> Most of the patients who experienced neutropenia were receiving taxanes and did not meet the criteria for primary prophylaxis per national guidelines. Therefore, we propose that the assessment of risk factors for neutropenia is critical in determining appropriate use of CSFs in patients with ESBC. Currently, our EMR system does not automatically screen for neutropenia risk factors. Until this function is automated, our nurses are using risk factor reference cards to identify patients who may need primary prophylaxis with CSFs.

We also observed that certain regimens were associated with greater reductions in RDI than others. Examples include: the paclitaxel portion of dose-dense AC followed by paclitaxel, and docetaxel/cyclophosphamide/trastuzumab. One patient had an RDI of less than 85% during dose-dense AC, and another patient who received doxorubicin with nanoparticle albumin-bound paclitaxel had a suboptimal RDI.

There are many opportunities for improving RDI in patients with adjuvant breast cancer. We believe nursing education is the most critical area that will directly affect outcomes. First, our collaborative nurses (nurse navigators) provide treatment calendars to patients with all expected dates of treatment before treatment initiation and provide education on the importance of receiving treatment on time. All patients attend a chemotherapy class in our office before their first treatment. This class has been revised to include a discussion on RDI and the importance of schedule adherence and minimization of chemotherapy-related complications. If a patient with ESBC requests a delay in treatment, a review process occurs before the delay is approved. This process includes communication between the treatment scheduler, collaborative nurse, and treating physician. If the treating physician is unavailable, the covering physician is informed of curative intent. Only the collaborative nurse can delay the treatment in our EMR system and on the patient calendar. In addition, we are now adding more details on the reasons for delays documented in our EMR. This will help us better understand specific



**Figure 6.** Patients without dose delay or reduction with relative dose intensity (RDI) > 85% in studies in community settings.

causes for delay on future analysis. Moving forward, we plan to include RDI as part of our new clinical staff orientation.

We found the RDI calculator provided by NearSpace to be user friendly, easily adaptable to our workflow, and an excellent tool for evaluating this quality measurement that meaningfully predicts long-term outcomes. Most quality measurements have questionable long-term benefit. We feel measuring RDI in the curative setting directly correlates to increased survivability in ESBC. We hope this process is exportable to other community-based practices to ensure higher RDI rates than those currently reported (Fig 6).

It is critically important to measure RDI when treating ESBC. Because the intent is curative in this setting, and adherence to an RDI of at least 85% correlates to increased OS and DFS rates, we were compelled to quantify our practice-wide RDI for this patient population. As part of a new quality initiative, we will continue to measure RDI so that we can optimize patient outcomes, prevent recurrent disease, and understand the factors that cause reductions to RDI in our community-based practice.

*Accepted for publication on August 18, 2009.*

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## Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None **Consultant or Advisory Role:** Robert L. Bretzel Jr, Amgen (U) **Stock Ownership:** None **Honoraria:** Robert L. Bretzel Jr, Amgen **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

Corresponding author: Robert L. Bretzel Jr, RPh, Fairfax Northern Virginia Hematology Oncology, 8503 Arlington Blvd, Ste 400, Fairfax, VA 22031; e-mail: robert.bretzel@usoncology.com.

DOI: 10.1200/JOP.091036; posted online ahead of print at <http://jop.ascopubs.org>.