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Original article

Variation in the use of granulocyte-colony stimulating factor for dose dense paclitaxel: A single institution retrospective study☆

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ABSTRACT

Introduction: The necessity of using granulocyte-colony stimulating factor (G-CSF) during dose-dense (DD) paclitaxel (T) after doxorubicin and cyclophosphamide (AC) is unclear.
Methods: This was a retrospective cohort study including patients with stage I-III breast cancer treated at Dana-Farber Cancer Institute with adjuvant DD-ACT between January 2011 and December 2013. Descriptive analyses evaluating patterns of G-CSF utilization during T were performed.
Results: Overall, 156 patients were treated with DD-ACT by 26 providers. The majority of patients (135, 87%) received at least one dose of G-CSF during T (group 1), 17% of these patients received it in only one cycle and 48% received it in all four cycles. Reasons for omitting G-CSF included high baseline absolute neutrophil count and pain. Twenty-one (13%) patients did not receive any G-CSF during T (group 2). Respectively, 94% and 90% of patients completed the treatment in groups 1 and 2. There were no cases of treatment cessation due to neutropenia. Six percent of patients in group 1 had at least one treatment delay. There were no treatment delays reported in group 2. Variation in the use of G-CSF by provider and by patient was found, with 11 providers choosing not to use G-CSF in at least one patient.
Conclusions: We identified substantial variation in the use of G-CSF within the practice. However, omission of G-CSF was not associated with treatment delays or adverse events. Prospective studies are warranted to formally test whether routine G-CSF is necessary during dose-dense T therapy.

Introduction

Over the last decades, breast cancer death rates have decreased in developed countries [1–3]. Adjuvant systemic treatments, including chemotherapy, have played a significant role in this trend. It has been estimated that adjuvant chemotherapy reduces the odds of death by 20–30% in women treated for early disease [4]. Improvements in the efficacy of adjuvant chemotherapy have been incremental and achieved through the addition of more active agents, as well as dose and schedule modifications (dose-intensity and dose-density) [5].

Dose-dense (DD) chemotherapy is defined as a treatment plan in which drugs are given with shorter time intervals between treatments when compared with standard chemotherapy. Its rationale has come from a mathematical model that predicts breast cancer growth by nonexponential Gompertzian kinetics [6]. For this reason, more frequent administration of cytotoxic therapy is postulated to be a more effective way of killing residual tumor burden [7]. After the pivotal phase III Cancer and Leukemia Group B 9741 trial established the superiority of a DD schedule of doxorubicin plus cyclophosphamide (AC) administered once every two weeks followed by paclitaxel (T) every two weeks in terms of improved disease-free survival (DFS) and overall survival (OS) among women with lymph node–positive breast cancer, this regimen became one of the standard adjuvant regimens to treat

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Abbreviations

DD	dose-dense
AC	doxorubicin plus cyclophosphamide
T	paclitaxel
G-CSF	granulocyte-colony stimulating factor
DFCI	Dana-Farber Cancer Institute
ANC	absolute neutrophil count
BMI	body mass index

patients with high-risk early breast cancer, and is included in National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines [8]. More recently, the GIM2 study, an Italian, randomized, phase 3 trial, confirmed the superiority of DD adjuvant chemotherapy over standard interval chemotherapy in terms of DFS, in patients with node-positive breast cancer [9]. Furthermore, two meta-analysis of randomized, phase 3 trials reinforced the superiority of DD chemotherapy compared with the non-DD schedules [10,11].

However, because neutropenia was the main limiting factor regarding DD chemotherapy, the development of this strategy was only possible with the use of granulocyte colony-stimulating factor (G-CSF) to accelerate bone marrow recovery. Clinical trials have not found differences in the rates of treatment delays and hematologic grade 3 and 4 adverse events in DD chemotherapy delivered with G-CSF support compared with non-DD chemotherapy schedules, and have established the safety and feasibility of DD chemotherapy [12,13]. Although G-CSFs are generally well-tolerated, they are not completely devoid of adverse effects, with the most common being medullar bone pain, reported in approximately 25–38% of patients [14]. In addition, prophylactic use of G-CSF is associated with substantial financial burden, both to patients and to the health care system. Indeed, utilization of these drugs represents the major driver of the variation among cancer treatment–related health care costs in early breast cancer in United States [15,16].

In a regimen such as DD-ACT, it is unclear whether T, which has a less myelosuppressive profile than AC, requires the routine use of growth factors for timely and safe administration [13,17]. In this study, we investigated the variation in the use of G-CSF, incidence of adverse events and scheduling impact of omitting G-CSF during the T portion of DD-ACT among patients treated with this regimen at our cancer center.

Material and methods

Patients and data sources

The current study evaluated patients with newly diagnosed stage I-III breast cancer defined by the American Joint Committee on Cancer seventh edition, who were treated with adjuvant DD-ACT at Dana-Farber Cancer Institute (DFCI) from January 2011 to December 2013. We identified the patient cohort by using an internal database developed as part of the National Comprehensive Cancer Network Opportunities for Improvement grant [18]. This study was conducted primarily by performing retrospective review of medical records; however we also used information generated by Research Patient Data Registry of Partner's Healthcare system and the CRIS (Clinical Research Information System)/oncDRS. Patients were not contacted as a part of this study. This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Outcomes and covariates

The primary outcome of interest in this study was the proportion of patients who did not receive G-CSF during the T portion of DD-ACT. The following subgroups were defined as group 1: patients treated with G-CSF, including patients who received G-CSF for at least one cycle while on the T portion of chemotherapy; group 2: patients not treated with G-CSF during any T cycle. Secondary outcomes included rates of T therapy completion, reasons T was discontinued, rates of dose delay, reasons for dose delay, median absolute neutrophil count (ANC) while on AC and while on T, variability in the use of G-CSF among medical oncologists, and reasons for avoiding G-CSF. Dose delays were defined as more than 14 days between day 1 of consecutive cycles. Neutropenia was defined is as an ANC of less than 1.0×10^9/L (<1000/μL).

Covariates

Information on tumor staging, tumor grade, hormone receptor status (HR), and HER-2 status were abstracted from pathology reports. Hormone receptor was considered positive if the estrogen and/or progesterone receptor were positive >1%. Tumor grade was categorized as high, intermediate or low, according to histological grade. The name of provider, age, body mass index (BMI) and comorbidity at diagnosis were abstracted by chart review.

Statistical analysis

Descriptive analyses were performed. The proportion of patients in group 1 and 2 was calculated. We then described demographics and pathological characteristics by treatment group (group 1 vs. group 2). Then, we summarized secondary outcomes by treatment group. Finally, we looked at treatment patterns by medical oncologist.

Results

Cohort characterization

Between January 2011 and December 2013, 523 patients with newly diagnosed breast cancer stage I-III received adjuvant chemotherapy at our institution. Among the 369 patients with HER2-negative disease, 156 (42%) patients were treated with DD-ACT and included in this analysis. During the T portion of treatment, 135 (87%) received at least one dose of G-CSF (group 1) and 21 (13%) did not (group 2). As shown in Table 1, patients had stage I (14%), II (61%), or III (25%) disease. Of note, the proportion of patients older than 60 years in groups 1 and 2 were, respectively, 16% and 28%. While in group 1, 38% of patients presented with comobidities, the rate in group 2 was 52%. In addition, prior delay of DD-AC due to neutropenia was uncommon in both groups. Table 1 also shows the clinicopathological characteristics of patients stratified by treatment group.

Treatment patterns by group

As shown in Table 2, eight patients (6%) in group 1 did not complete four cycles of T: five patients stopped their adjuvant treatment due to neuropathy (two after the first and three after the second cycle); one had a severe hyper sensitivity reaction after the first T infusion, one had an acute coronary syndrome after second cycle and the other did not receive the last two cycles due unknown reasons. No patients discontinued T due to neutropenia. Eight (6%) patients had at least one treatment delay, including two due to neutropenia without fever, and one due to febrile neutropenia. In