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SHORT COMMUNICATION



Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice—an updated analysis

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KEY WORDS

Febrile neutropenia, breast cancer, adjuvant chemotherapy

1. INTRODUCTION

Chemotherapy in the adjuvant setting for early breast cancer (EBC) has improved disease-free and overall survival, with benefits extended to elderly patients and to those with lymph-node-negative pathology[1,2]. Recent clinical trials have largely supported the additional benefit of taxane therapy, including benefit in older patients[3]. The increase in the proportion of women treated and the improved survival mean that toxicities become increasingly important. One of the most serious acute toxicities is febrile neutropenia (FN). An updated U.S. Oncology trial report has demonstrated benefit in disease-free and overall survival for 4 cycles of docetaxel–cyclophosphamide (TC) chemotherapy over doxorubicin–cyclophosphamide chemotherapy and has also reported acceptable toxicity, with a FN rate of 5%[4]. The TC regimen has become very popular in Ontario, particularly in older age groups who are at increased risk of cardiotoxicity with anthracyclines and in patients eligible for trastuzumab[5].

We previously published our experience with EBC patients treated with TC chemotherapy and the incidence of FN[6]. Here, we present our updated and expanded data examining the incidence of FN related to the use of TC chemotherapy in the adjuvant setting in EBC at the London Regional Cancer Program.

2. METHODS

This update includes a consecutive series of 134 patients treated with 4 cycles of TC from January 2008 to August 2011 and assessed by retrospective chart review as a quality assurance tool.

These women all had early-stage (high-risk node-negative; node-positive; or T1, 2, or 3; but not locally advanced or inflammatory) breast cancer and were treated with docetaxel 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles. All patients were evaluable for review and analysis after completion of the prescribed treatment (admissions may have been at our host hospital or at a community hospital) and include those who stopped treatment early.

Medical records for all hospitals in the region except 1 are available via electronic health record, and discharge summaries were available for all patients admitted with FN. Our institution defines FN as a temperature of 38.0°C, at which point the patient is instructed to seek emergency medical assessment, including clinical assessment and complete blood count by a physician. The standard definition of neutropenia is a cell count below 0.5×10^9/L or below 1.0×10^9/L and expected to worsen.

3. RESULTS

In this group of patients, median age was 61.5 years (range: 33–84 years). Comorbidities were present in 71 patients (examples include, but are not limited to, diabetes mellitus, pulmonary embolism, prior chemotherapy, Crohn disease, rheumatoid arthritis, interstitial cystitis, atrial fibrillation, sleep apnea, hypertension, and delayed wound healing), and 71 patients had received primary prophylaxis with filgrastim or pegylated filgrastim. Three patients were unable to complete treatment, and no patient was lost to follow up. Table I summarizes the FN rate in these patients overall and by subgroup.

The FN rate was 20% across all patients (27 of 134). Of the 71 patients who received primary prophylaxis, only 3 experienced FN (4.2%). For patients not receiving primary prophylaxis, the FN rate was 38% (24 of 63). A total of 53 patients in this study (40%) were 65 years of age or older. The incidence of FN in that group reached 26.4%. Among the 27 patients who developed FN, 14 were 65 years of age or older (51.8%). Of the 3 patients who stopped treatment early, 1 had FN.

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TABLE I Age group, comorbidities, use of granulocyte colony–stimulating factor (G-CSF), and incidence of febrile neutropenia (FN)

Group	*Pts* (n)	*FN rate*	
		(%)	*Given G-CSF*[a] (n)
Age < 65 years			
Without comorbidities	41	17	21
With comorbidities	40	15	29
Age > 65 years			
Without comorbidities	22	23	8
With comorbidities	31	29	13

[a] Only 3 patients of 71 given primary prophylaxis with G-CSF developed FN.
Pts = patients.

4. DISCUSSION AND CONCLUSIONS

We previously published an increased FN rate of 33% in a series of 39 patients treated in the adjuvant setting with TC chemotherapy for EBC[6]. The FN rate rose further to 46% in patients without primary prophylaxis. We updated our database to include 134 consecutive patients treated with TC chemotherapy, and we still observed a higher-than-expected FN rate: 38% without and 4.2% with primary prophylaxis. Based on our updated series of patients, it appears that TC chemotherapy is associated with a higher rate of FN than has been published or reported. No patient died or required intensive care as a result of FN complications in our series. Our case series now has 71 patients with primary prophylaxis and 63 patients without prophylaxis, providing a reasonable comparison between patients who received primary prophylaxis with treatment and those who did not. Although this higher FN rate may have several underlying factors, our rate may be the result of treatment in a population older or with more comorbidities than is usually entered into a clinical trial, which is consistent with risk factors from the National Comprehensive Cancer Network and the American Society of Clinical Oncology guidelines[7,8].

We used age 65 as a benchmark because our provincial government health insurance does not cover supportive care drug costs for outpatients younger than 65 years and also because age 65 is considered a risk factor for FN. The average age in the U.S. Oncology trial was 52 years compared with the 61.5 years seen in our cohort. Interestingly, the risk of FN also seems high in the younger group treated with TC chemotherapy. Furthermore, we suspect that primary prophylaxis is underreported. The initial report of TC[9] did not mention whether primary prophylaxis was used; the subsequent report indicated that prophylactic quinolones were recommended (but not required) and did not mention how many patients were given prophylactic antibiotics. More recently, in the first cycle only, the FN incidence in that trial was reported to be 2.8% with primary prophylaxis, which increased to 9.5% without it[10]. Our data are consistent with those from another report[11] that showed a significant difference in the rate of FN with (8.6%) or without (24.5%) primary prophylaxis during adjuvant TC chemotherapy. Finally, a recent meta-analysis[12] looking at 902 patients treated with TC chemotherapy estimated the FN rate to be 29% without primary prophylaxis.

We feel that age, comorbidities such as diabetes[13], and less-routine use of prophylaxis are significant factors increasing the risk of FN. Although primary prophylaxis with granulocyte colony–stimulating factors has little effect on mortality from FN[14], our experience should serve to encourage more consistent and complete reporting of supportive care drugs and comorbidities when assessing the toxicities of adjuvant chemotherapy. Our rate of FN, which is consistent with those in other reports and meta-analyses, argues for a greater role for primary prophylaxis in patients treated with TC chemotherapy for EBC.

5. CONFLICT OF INTEREST DISCLOSURES

JY has received speakers' honoraria in the past from Amgen. The remaining authors have no financial conflicts of interest to declare.

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