Journal of Integrative Oncology
ISSN: 2329-6771

Gagliato et al., J Integr Oncol 2017, 6:3
DOI: 10.4172/2329-6771.1000195

Research Article Open Access

Febrile Neutropenia Risk with Adjuvant Docetaxel and Cyclophosphamide (TC) Chemotherapy Regimen in Two Brazilians Cancer Centers

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Received Date: June 16, 2017; **Accepted Date:** June 28, 2017; **Published Date:** June 30, 2017

Abstract

Introduction: In selected patients diagnosed with Breast Cancer (BC), adjuvant chemotherapy might reduce local and systemic recurrence risk, as well as cancer death rate. The combination of Docetaxel and Cyclophosphamide (TC) is a well-recognized effective adjuvant chemotherapy regimen. Nonetheless, a considerable high rate of febrile neutropenia (FN) is associated with this regimen. We sought to investigate hematologic toxicity associated with adjuvant TC in a non-selected, "real world" cohort of BC patients.

Methods: We reviewed the electronic medical records of patients who presented to the Oncology Center from Hospital Sírio-Libanês (HSL) and Instituto do Câncer do Estado de Sao Paulo (ICESP). Patients included in the analysis received adjuvant chemotherapy with TC regimen after definitive breast surgery.

Results: 95 patients with were included in our analysis. Median age was 55.5 years. All patients had a good performance status (either ECOG 0 or 1), and the great majority had no comorbidities. Most patients received 4 cycles of chemotherapy (80%). Data on granulocyte colony stimulating factor (G-CSF) administration was available in 85 patients from our cohort. G-CSF was used as primary prophylaxis in 31 patients, and as secondary prophylaxis in 13 patients, following a prior episode of febrile neutropenia. Overall, fifteen women (15.8%) had a documented FN episode. Among women who received G-CSF as primary prophylaxis, the rate of FN was 6.45% (2 patients). In contrast, among patients who did not receive primary prophylaxis with G-CSF, FN rate was considerably higher, namely 24.07% (13 patients). Patients who received primary prophylaxis with G-CSF had a statistically significant lower risk of experiencing a FN episode (p=0.049).

Conclusion: Febrile Neutropenia rate in this group of non-selected BC patients was higher than previous reported on randomized controlled trials that evaluated adjuvant TC regimen in the same dosing and schedule as used in our cohort. Primary prophylaxis with G-CSF was associated with a statistically significant lower risk of FN and should be considered in the management of patients who receive this chemotherapy combination.

Keywords: Breast cancer; Adjuvant chemotherapy; Febrile neutropenia; G-CSF prophylactic therapy

Introduction

Adjuvant cytotoxic treatment in Breast Cancer (BC) patients refers to chemotherapy treatment administration after breast definitive surgery, aiming to reduce the risk of breast and systemic recurrence, as well as cancer death. This therapy approach improves outcomes in selected patients with early BC [1,2]. Traditionally, decision of whether to treat patients with early stage BC has been based on clinicopathologic parameters, such as tumor size or nodal involvement extent [3,4]. Recently, genomic tools, such as Oncotype Dx score has also been used as an important tool to predict prognosis, and also chemotherapy benefit in node negative, estrogen receptor–positive BC patients [5].

Exposure to chemotherapy cytotoxic agents may lead to both early and late toxicities. Of note, one of the most common toxicity observed among breast cancer survivors is left ventricular dysfunction [6]. Anthracycline-mediated cardiotoxicity frequently occurs after one year since treatment completion, usually tends to be irreversible and is related to cumulative anthracycline dose [7].

Anthracycline containing combinations in the adjuvant treatment for operable breast cancer is proven to reduce relapse and breast cancer death, irrespective of estrogen receptor (ER) status, nodal status and adjuvant hormone therapy use [1]. Taxanes were added in BC adjuvant treatment and were associated with improved survival outcomes in comparison with anthracyclines alone [8-11]. Currently, anthracyclines are being replaced by taxanes in BC adjuvant treatment, especially among patients with node negative, hormone receptor positive BC who a clinical or genomic risk that justifies adjuvant chemotherapy. Nevertheles, a recent series of three adjuvant trials demonstrated that an anthracycline taxane based chemotherapy improved Invasive disease survival compared to a taxane only chemotherapy [12].

A taxane only based adjuvant chemotherapy regimen has the potential to avoid rare, but very serious side effects associated with anthracyclines, such as cardiotoxicity, secondary acute myeloid leukemia and myelodysplastic syndrome [13,14]. Besides, another major advantage is the avoidance of gastrointestinal symptoms associated with doxorubicin, especially nausea and vomiting.

US Oncology 9735 (USO-9735) was a remarkable trial that established taxane efficacy over anthracycline. This trial compared 4 cycles of Doxorubicin and Cyclophosphamide (AC) with four cycles of Docetaxel and Cyclophosphamide (TC) in the adjuvant setting. The taxane containing regimen was associated with superior Event Free Survival (EFS), namely 81% for TC versus 75% for AC (p=0.033; Hazard Ratio [HR]=0.74; 95% CI 0.56 to 0.98). 14 After 7 years of follow up, it was also demonstrated a significant survival benefit favoring TC (87% vs. 82%, p=0.032; HR=0.69; 95% CI 0.50 to 0.97) [15].

Of note, toxicity profile from each of these regimens was quite different. AC regimen was associated with more nausea and vomiting, one cardiac death from congestive heart failure and four from myocardial infarction. In contrast, patients who received TC experienced more febrile neutropenia (FN), as well as more grade 1 and 2 peripheral edema, myalgia, and arthralgia (p<0.01). One toxic death due to febrile neutropenia occurred in the TC arm.

Febrile neutropenia (FN) was an important toxicity associated with TC treatment and occurred in 5% of patients in this arm. For patients with 65 years old or more, the febrile neutropenia rate was increased to 8%, compared with 4% in patients younger than 65 years old. Of note, no prophylactic granulocyte colony-stimulating factor (G-CSF) was used in this study. Nevertheless, it was strongly recommended prophylactic oral antibiotics use, and although the Original Manuscript does not precisely describe the rate of patients prophylactically treated with oral antibiotics, it is mentioned that it was indeed prescribed to a great number of patients during hematologic nadirs.

We sought to investigate hematologic toxicity associated with adjuvant TC chemotherapy in a cohort of BC patients treated at Hospital Sírio-Libanês (HSL) and Instituto do Câncer do Estado de São Paulo (ICESP). We were particularly interested in observing the neutropenia rate and FN events in a non-selected group of women, representing the day-to-day patient treated with adjuvant TC.

Patients and Methods

Study design

We performed a retrospective analysis to identify patient's characteristics that could be associated with a higher risk of FN in patients with Breast Cancer who received adjuvant TC regimen (Docetaxel and Cyclophosphamide). Correlation between FN risk and G-CSF prophylactic administration was also analyzed.

Patient selection

Patients who presented to the Oncology Center from Hospital Sírio-Libanês (HSL) and Instituto do Câncer do Estado de Sao Paulo (ICESP) after definitive breast surgery from March 2000 through June 2013 and were treated with adjuvant TC regimen were included in our analysis. A retrospective review of the medical records charts from these patients was performed.

Data abstracted included age at diagnosis; race; BMI (body mass index); performance status (ECOG); associated comorbidities; tumor pathological staging; tumor grade and histology, neutropenia and FN rates, use of granulocyte colony stimulating factor (G-CSF), either before (primary prophylaxis) or after a documented FN event (secondary prophylaxis). Data on other previous chemotherapy for the current BC diagnosis as well as cytotoxic chemotherapy treatment for other previous malignancies were also collected. The Institutional Review Board of Hospital Sírio-Libanês and ICESP approved this study.

Statistical analysis

Patient characteristics were summarized using frequency distributions and percentages. All statistical analyses were carried out using SPSS for Windows Version 13.0. Chi square test was used to correlate a FN episode with the categorical variables. Binomial test was used to compare proportions in one sample. Student's t-test was elected to equate a FN episode in relation to numerical categories. We considered a p-value less than 0.05 to be statically significant.

Results

Patient population

We identified 102 patients who had BC diagnosis and were treated with the TC chemotherapy regimen. Four patients were excluded due to a later finding of metastatic disease. Additionally, in three patients it was not clear if there was a FN event, thus those patients were excluded from the study. After excluding those individuals, analysis was performed in 95 women. Among these patients, 66 were treated at HSL and 29 at ICESP.

Median age was 55.5 years (range 31.4–85.1). All patients had a good performance status (ECOG 0 or 1) and the great majority had none or only one comorbidity. This is shown in Table 1.

Variables	Total
Neutropenic Fever	
1-Yes	15 (15.8%)
2-No	80 (84.2%)
Total	95 (100%)
Second Neutropenic Fever Episode	
2-No	15 (100%)
Total	15 (100%)
G-CSF	
1-Yes	44 (51.8%)
2-No	41 (48.2%)
Total	85 (100%)
G-CSF Primary versus Secondary prophylaxis	
1-Primary	31 (70.5%)
2-Secondary	13 (29.5%)

Total	44 (100%)
Age at first evaluation	
Mean (SD)	55.5 (10.7)
Median (Min; Max)	56.2 (31.4; 85.1)
Total	92
Age at diagnosis	
Mean (SD)	54.9 (10.5)
Median (Min; Max)	55.5 (31.2; 84.9)
Total	92
Body Mass Index (BMI)	
Mean (SD)	26 (4.2)
Median (Min; Max)	25 (18.4; 37.6)
Total	93
Chemotherapy Cycles	
Mean (SD)	3.8 (1.1)
Median (Min; Max)	4 (1; 6)
Total	95
Cycles	
1	7 (7.4%)
2	5 (5.3%)
4	76 (80%)
5	1 (1.1%)
6	6 (6.3%)
Total	95 (100%)
Cycle (FN)	
Mean (SD)	1.6 (1.4)
Median (Min; Max)	1 (1; 6)
Total	15
Cycle (FN)	
1	11 (73.3%)
2	2 (13.3%)
3	1 (6.7%)
6	1 (6.7%)
Total	15 (100%)
ECOG Performance Status	
0	76 (83.5%)
1	15 (16.5%)
Total	91 (100%)
Comorbidities	
Mean (SD)	1.1 (1.1)
Median (Min; Max)	1 (0; 4)
Total	64
Comorbidities	
0	25 (39.1%)
1	20 (31.3%)
2	10 (15.6%)
3	7 (10.9%)
4	2 (3.1%)
Total	64 (100%)
Previous treatment for the current diagnosis	
1-Yes	4 (4.2%)
2-No	91 (95.8%)
Total	95 (100%)
Previous treatment for other malignancies	
1-Yes	8 (8.4%)
2-No	87 (91.6%)
Total	95 (100%)
G-CSF- Granulocyte Colony Stimulating Factor; Min-Minimum; Max- Maximum	

Table 1: Variables descriptive analysis.

The great majority of patients, namely 83 (87.36%), had never received any oncologic treatment before adjuvant TC. The remaining 12 patients received at least one medical oncologic treatment before TC regimen. Among those, eight were treated for other previous malignancies with distinct chemotherapy regimens. Four patients received therapy for a previous BC diagnosis. Of note, one of them had received tamoxifen. Another patient was treated with frontline CAF, subsequently developing a FN episode. In this particular case, the leading physician chose to change therapy to TC regimen. The vast majority of individuals (80%) received all four-planned chemotherapy cycles, contrasting with one (1.1%) and six (6.3%) patients who received five and six cycles of TC, respectively.

FN episode and G-CSF use

Among the 95 patients included in our analysis, data on G-CSF administration was available in 85 of them. G-CSF was used as primary prophylaxis in 31 (70.5%) patients and in 13 patients as secondary prophylaxis, following a prior diagnosis of febrile neutropenia.

Primary G-CSF	Neutropenic fever			p-value
	1-Yes	2-No	Total	
1-Yes	2 (13.3%)	29 (41.4%)	31 (36.5%)	0.049*

2-No	13 (86.7%)	41 (58.6%)	54 (63.5%)	
Total	15 (100%)	70 (100%)	85 (100%)	

Table 2: Neutropenic fever episode and G-CSF Treatment.

Overall, fifteen women (15.8%) had a documented FN episode. Among women who received G-CSF as primary prophylaxis, the rate of FN was 6.45% (2 patients). In contrast, among patients who did not receive primary prophylaxis with G-CSF, the FN rate was considerably higher, namely 24.07% (13 patients). Patients who received primary prophylaxis with G-CSF had a statistically significant lower risk of experiencing a FN episode (p=0.049). Table 2 demonstrates this finding.

We could not identify any patient clinical characteristic nor previous chemotherapy treatment that could be correlated with an increased FN risk. This is shown in Table 3.

Variables Stratified by NF Occurrence	**Yes**	**No**	**Total**	**p-value**
Age (Initial Appointment)				
Mean (SD)	56.17 (12.34)	55.38 (10.45)	55.51 (10.71)	0.794*
Median (Min-Max)	56.19 (33.98-85.07)	56.25 (31.4-77.54)	56.22 (31.4-85.07)	
Total	15	77	92	
Age (Diagnosis)				
Mean (SD)	54.55 (12.06)	54.92 (10.3)	54.86 (10.54)	0.902*
Median (Min-Max)	56.19 (33.97-84.9)	55.09 (31.22-77.46)	55.47 (31.22-84.9)	
Total	15	77	92	
BMI				
Mean (SD)	25.82 (3.13)	26.04 (4.42)	26.01 (4.23)	0.853*
Median (Min-Max)	25.7 (21.8-31.5)	24.9 (18.4-37.6)	25 (18.4-37.6)	
Total	15	78	93	
Cycles				
Mean (SD)	3.6 (1.3)	3.85 (1.01)	3.81 (1.05)	0.402*
Median (Min-Max)	4 (1-6)	4 (1-6)	4 (1-6)	
Total	15	80	95	
Cycles				
1	2 (13.3%)	5 (6.3%)	7 (7.4%)	0.872***
2	1 (6.7%)	4 (5%)	5 (5.3%)	
4	11 (73.3%)	65 (81.3%)	76 (80%)	
5	0 (0%)	1 (1.3%)	1 (1.1%)	
6	1 (6.7%)	5 (6.3%)	6 (6.3%)	
Total	15 (100%)	80 (100%)	95 (100%)	
Cycle				
Mean (SD)	1.6 (1.35)	1.23 (0.44)	1.43 (1.03)	0.356*
Median (Min-Max)	1 (1-6)	1 (1-2)	1 (1-6)	
Total	15	13	28	
Cycle				
1	11 (73.3%)	10 (76.9%)	21 (75%)	0.411***

2	2 (13.3%)	3 (23.1%)	5 (17.9%)	
3	1 (6.7%)	0 (0%)	1 (3.6%)	
6	1 (6.7%)	0 (0%)	1 (3.6%)	
Total	15 (100%)	13 (100%)	28 (100%)	
Comorbidities				
Mean (SD)	1.64 (1.36)	0.96 (1.06)	1.08 (1.13)	0.072*
Median (Min-Max)	2 (0-4)	1 (0-4)	1 (0-4)	
Total	11	53	64	
Comorbidities				
0	3 (27.3%)	22 (41.5%)	25 (39.1%)	0.404***
1	2 (18.2%)	18 (34%)	20 (31.3%)	
2	3 (27.3%)	7 (13.2%)	10 (15.6%)	
3	2 (18.2%)	5 (9.4%)	7 (10.9%)	
4	1 (9.1%)	1 (1.9%)	2 (3.1%)	
Total	11 (100%)	53 (100%)	64 (100%)	
ECOG Performance Status				
0	12 (85.7%)	64 (83.1%)	76 (83.5%)	1.000**
1	2 (14.3%)	13 (16.9%)	15 (16.5%)	
Total	14 (100%)	77 (100%)	91 (100%)	
*Student's t test; **Fisher's exact test; ***Likelihood ratio test				

Table 3: Clinical characteristics and neutropenic fever risk.

Discussion

In this retrospective analysis from BC patients treated in the adjuvant setting with TC chemotherapy regimen, we demonstrated that primary prophylaxis with G-CSF was associated with a statistically significant lower risk of developing FN. Of note, even this favorable group of patients, in which performance status and preexisting comorbidities factors were quite propitious, G-CSF was still effective in preventing this potentially life threating outcome.

Maintenance of a dose intensity treatment, namely chemotherapy dosing and interval timing administration, is of great importance is obtaining the maximum benefit from adjuvant treatment. Previous trials have clearly demonstrated a correlation between dose intensity and BC survival outcomes [16,17]. Hryniuk et al. showed that chemotherapy dose intensity was an independent predictor of Relapse Free Survival, irrespective of age and lymph node involvement [18].

Notably, neutropenia is the most frequently major dose-limiting toxicity of chemotherapy and the primary driver of the dose delays and reductions that might result in drug dosing impairment. It is intuitive to establish a threshold for dose reduction, beyond which chemotherapy efficacy might be compromised. In a real world population treated in two of the most notables Cancer Centers from Brazil, we found a much higher rate of FN associated with TC compared to the USO-9735 trial (15.8% versus 5%, respectively). This reflects that the outcomes found in randomized controlled trials may not be transposed with maximum fidelity to day-to-day clinic.

In order to identify which group of patients would be at increased risk of dose reduction, Lyman et al performed a survey of 1,243 community oncology practices in the United Stated of America. They were able to find that older patients were at a particularly higher risk for dosing modification due to adverse side effects associated with chemotherapy, especially neutropenia [19].

Contrary to other trials, we were not able to identify a subgroup of patients who were at a particularly higher risk for a FN event. Age was not a risk factor for FN in our patient cohort population. In contrast, patients older than 65 years in the USO-9735 trial were almost twice more likely to experience a FN event compared to younger patients. Other classic risk factor for FN, such as tumor bone marrow involvement, prior myelosuppressive therapy and concomitant or prior radiation therapy [20], were not present in our population.

Primary prophylaxis with G-CSF was highly effective in preventing FN. Compared to patients who did not receive G-CSF, those treated with filgrastin had a statistically significant lower incidence of FN in our study (24.07% versus 6.45%, respectively). In accordance with a previous systematic review, prophylactic G-CSF was associated with a reduced risk of FN. This meta-analysis was the first study that

demonstrated an association with filgrastin use and reduction in risk of infection-related mortality as well as early deaths [21].

The American Society of Clinical Oncology (ASCO) recommends using G-CSF as primary prophylaxis when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20% [22,23]. Nevertheless, it is clearly emphasized that patient individualization, taking into account individual patient risk factors for FN, should be a crucial factor in determining white blood cell growth factors use, even in chemotherapy regimens that have a lower chance of causing febrile neutropenia.

Also, 2015 ASCO Guideline Recommendations for the Use of white blood cell growth factors emphasize that some factors might be associated with poor clinical outcomes after an infection or febrile neutropenia, such as older age, profound neutropenia, hospitalization at the time of fever, among others [23]. Avoidance of such complications with primary prophylaxis with G CSF might be carefully considered, since performance status and capability to receive adequate doses of chemotherapy might be compromised as a consequence of previous infection or febrile neutropenia episode.

Additionally, previous analysis of cost effectiveness of Primary versus Secondary Prophylaxis with G-CSF in women with early stage BC receiving chemotherapy, demonstrated that primary prophylaxis may be equivalent or superior in cost effectiveness to other commonly used supportive care interventions for FN treatment [24]. Other reports also corroborate clinical and economic benefits from prophylactic administration of G-CSF [25,26].

In summary, we demonstrated that in a non-selected group of patients receiving adjuvant TC chemotherapy, FN was a major side effect from treatment. Primary prophylaxis with G-CSF was highly effective in preventing this potentially harmful adverse event. In clinical practice, physicians should carefully evaluate their patients, prioritizing strategies to minimize the risk of chemotherapy dose intensity reduction. From this viewpoint, primary prophylaxis with G-CSF is a reasonable available resource and might be considered in patients receiving TC chemotherapy.

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