Effects of primary granulocyte-colony stimulating factor prophylaxis on neutropenic toxicity and chemotherapy dose delivery in Chinese patients with breast cancer who received adjuvant docetaxel plus cyclophosphamide chemotherapy: a retrospective cohort study

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ABSTRACT

Introduction: This study was performed to examine the effects of primary granulocyte-colony stimulating factor (G-CSF) prophylaxis on neutropenic toxicity, chemotherapy delivery, and hospitalisation among Chinese patients with breast cancer in Hong Kong.

Methods: This retrospective study included patients with breast cancer who received adjuvant docetaxel plus cyclophosphamide chemotherapy from November 2007 to October 2013 at Princess Margaret Hospital. Data were collected regarding the usage of G-CSF prophylaxis; incidences of grade 3 or 4 neutropenia, febrile neutropenia, non-neutropenic fever, and infection; hospital admissions, and chemotherapy dose delivery. Patients who began to receive G-CSF prophylaxis during the first cycle of chemotherapy and continued such prophylaxis in subsequent cycles were regarded as the primary G-CSF prophylaxis group.

Results: In total, 231 female Chinese patients with breast cancer were included in the analysis. Overall, 193 (83.5%) patients received primary G-CSF prophylaxis. The demographics and tumour characteristics were comparable between patients with and without primary G-CSF prophylaxis. Primary G-CSF prophylaxis significantly reduced febrile neutropenia incidence from 31.6% to 14.5% (relative risk=0.45, 95% confidence interval=0.25-0.81). Primary G-CSF prophylaxis also significantly reduced the incidence of grade 3 or 4 neutropenia from 57.9% to 24.7% (relative risk=0.43, 95% confidence interval=0.30-0.62) and the incidence of febrile neutropenia–related hospital admission from 31.6% to 12.4% (P=0.025). Finally, it enabled more patients to receive adequate chemotherapy dose delivery.

Conclusion: Primary G-CSF prophylaxis effectively reduced the incidences of grade 3 or 4 neutropenia and febrile neutropenia, while enabling adequate chemotherapy dose delivery and reducing hospital admissions among Chinese patients with breast cancer who received adjuvant docetaxel plus cyclophosphamide chemotherapy.

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New knowledge added by this study

- Primary granulocyte-colony stimulating factor (G-CSF) prophylaxis was associated with reduced neutropenic toxicity from adjuvant docetaxel plus cyclophosphamide (TC) chemotherapy.
- Our 4-day G-CSF schedule helped to maintain the planned chemotherapy regimen and reduce the rate of hospital admission.

Implications for clinical practice or policy

- Routine use of primary G-CSF prophylaxis enabled successful chemotherapy treatment and adequate chemotherapy dose delivery for patients with early breast cancer who received adjuvant TC chemotherapy.
- Primary G-CSF prophylaxis could reduce hospital admissions for the management of febrile neutropenia; it may reduce in-patient bed occupancy and offset hospitalisation costs.
- G-CSF prophylaxis can be extended to patients on all docetaxel-containing regimens of neoadjuvant and adjuvant chemotherapy.

預防性使用粒細胞集落刺激因子對接受多西紫杉醇聯合環磷酰胺輔助化療的中國香港乳腺癌患者的中性粒細胞毒性反應和化療劑量的影響：回顧性隊列研究

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目的：檢視中國香港女性乳腺癌患者預防性使用粒細胞集落刺激因子（G-CSF）對因接受化療出現的中性粒細胞毒性反應、進行化療和住院的結果。

方法：這項回顧性研究納入從2007年11月至2013年10月期間，於香港瑪嘉烈醫院接受多西紫杉醇聯合環磷酰胺（TC）輔助化療的乳腺癌患者。從臨床記錄和化療簡表收集的數據包括預防性使用G-CSF、3-4級中性粒細胞減少症、發熱性中性粒細胞減少症、非中性粒細胞減少症發熱和感染的發生率，以及入院和化療劑量。自化療第一周期開始接受G-CSF預防並在隨後周期繼續使用被定義為預防性使用G-CSF。

結果：231名中國香港女性乳腺癌患者被納入分析。193名（83.5%）患者接受預防性G-CSF注射。比較接受和未接受預防性G-CSF注射的患者，兩組的人口統計資料和腫瘤特徵相若。預防性使用G-CSF可使發熱性中性粒細胞減少症的發生率從31.6%降至14.5%（相對危險度=0.45，95%置信區間=0.25-0.81）。預防性使用G-CSF也將3-4級中性粒細胞減少症的發生率從57.9%顯著降低至24.7%（相對危險度=0.43，95%置信區間=0.30-0.62），而發熱性中性粒細胞減少症相關的住院率則從31.6%降低至12.4%（P=0.025），並使更多患者接受足夠劑量化療。

結論：預防性使用G-CSF有效降低採用輔助TC方案治療的乳腺癌患者的3-4級中性粒細胞減少症和發熱性中性粒細胞減少症的發生率；它可使患者接受足夠劑量的化療，以及減低入院率。

Introduction

Adjuvant chemotherapy significantly improves disease-free survival and overall survival in patients with early breast cancer.[1] For intermediate-risk patients who have axillary lymph node-negative early breast cancer,[2] a common regimen comprises four cycles of doxorubicin plus cyclophosphamide. In 2009, Jones et al[3] published a 7-year follow-up study of patients with stages I-III operable breast cancer in the United States; they reported that superior disease-free survival and overall survival could be achieved with four cycles of docetaxel plus cyclophosphamide (TC), compared with four cycles of doxorubicin plus cyclophosphamide. Since then, TC has been increasingly regarded as an alternative chemotherapy regimen to doxorubicin plus cyclophosphamide for patients with early-stage breast cancer. However, docetaxel causes significant myelotoxicity, characterised by high incidences of grade 3 or 4 neutropenia and febrile neutropenia (FN). Chemotherapy-induced neutropenia is a major type of toxicity that limits the dose of cancer therapy; FN is associated with substantial morbidity, mortality, and financial costs.[4] Febrile neutropenia is considered a medical emergency, which often requires immediate hospitalisation and empirical administration of broad-spectrum antibiotics. Severe (grade 3 or 4) neutropenia or FN is the most common cause of dose reductions and/or cycle delays that lead to lower chemotherapy dose intensity; such changes may influence clinical outcomes, particularly when treatment is intended to be curative or to prolong survival.[5,6]

There is substantial evidence that granulocyte-colony stimulating factor (G-CSF) prophylaxis reduces the incidence of chemotherapy-associated FN in patients with diverse malignancies, including patients with breast cancer who are receiving chemotherapy and have moderately high/high FN risk; this prophylaxis can result in fewer chemotherapy dose reductions or delays.[5,7-9] Current guidelines consistently recommend G-CSF prophylaxis during chemotherapy treatment for patients with cancer who have a high estimated risk of FN (ie, approximately 20%), as well as patients with cancer who have a history of FN.[5,10-12] The administration of G-CSF should also be used to facilitate the maintenance of chemotherapy dose intensity for patients in whom reduced chemotherapy dose intensity or density is likely to cause a poor outcome (eg, patients receiving adjuvant or potentially curative treatment, or patients receiving treatment to prolong survival).[5,10,12]

We began using TC chemotherapy in 2007 at Princess Margaret Hospital, but we encountered a high incidence of FN. Our initial solution comprised dose reduction; after the first episode of FN, doses of chemotherapeutic agents were reduced by 10% to 25% in subsequent cycles. Then, G-CSF prophylaxis was administered if the second episode of FN occurred to avoid further dose reduction and to ensure delivery of planned chemotherapy; it was also intended to prevent the occurrence of further FN. This study was conducted to investigate the effects of primary G-CSF prophylaxis on neutropenic toxicity, chemotherapy delivery, and hospitalisation in patients with breast cancer if G-CSF was administrated from the first cycle of TC chemotherapy.

Methods

Patient selection

This retrospective cohort study was performed at Princess Margaret Hospital, Hong Kong. We reviewed the medical records of female Chinese patients with breast cancer who received adjuvant TC chemotherapy from November 2007 to October 2013. Exclusion criteria were as follows: previous receipt of chemotherapy, mixed TC and doxorubicin plus cyclophosphamide or other chemotherapy

regimens; more than four cycles of TC; failure to complete four cycles of chemotherapy; and use of G-CSF after the occurrence of FN. Data were retrieved from the included patients' out-patient and in-patient records, chemotherapy charts, and discharge summaries.

Tumour characteristics

Tumour staging, histological type, histological grade, lymphovascular invasion, oestrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 (HER2) status, and Ki67 status were extracted from each patient's pathology report. Oestrogen and/or progesterone receptor statuses were considered positive if either percentage of immunohistochemical staining was ≥1% (ie, an H score of ≥50 or an Allred score of ≥3). The HER2 status was considered positive if the immunohistochemical score was 3, or if fluorescence in situ hybridisation showed HER2 gene amplification if immunohistochemical score was equivocal.

Docetaxel plus cyclophosphamide treatment protocol

Chemotherapy was initiated within 6 to 8 weeks after surgery. The chemotherapeutic regimen consisted of docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 administered by intravenous infusion over 60 minutes and 30 minutes, respectively, on day 1 at 3-week intervals for four cycles; dexamethasone premedication and standard anti-emetic were administered during each cycle. In accordance with standard protocol in the Department of Oncology at Princess Margaret Hospital, patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1. At baseline and before each cycle of chemotherapy, complete blood counts were performed, along with tests of renal and hepatic function. To proceed with treatment, patients were required to have a white blood cell count of ≥3 × 10^9/L, an absolute neutrophil count (ANC) of ≥1.5 × 10^9/L, and a platelet count of ≥100 × 10^9/L. For patients with insufficient blood counts, chemotherapy was deferred for ≥1 week until counts reached the required levels. For patients with an elevated alanine transaminase level (ie, ≥1.5-fold above the upper limit of normal), the dose of docetaxel was reduced by 15%, in accordance with prescribing information. Complete blood counts were also checked at nadir (ie, the lowest white blood cell count or ANC recorded within 21 days of the first cycle of chemotherapy, typically on day 10 after chemotherapy) to assess the severity of neutropenia; based on blood count findings, chemotherapy dosage was adjusted (if necessary) in subsequent cycles. The dosage reduction ranged from 10% to 25% according to the occurrence of grade 4 neutropenia or FN in prior cycles. Hepatitis status was checked at baseline. Prophylactic antiviral therapy was administered to patients who had a positive test result for hepatitis B surface antigen.

Granulocyte-colony stimulating factor use

We suggested G-CSF prophylaxis (on a self-financed basis during the study period) to each patient who was scheduled to receive adjuvant TC, unless they had contra-indications mentioned in the prescribing information. The intent of G-CSF prophylaxis was to prevent the occurrence of FN, which would lead to cycle delay and chemotherapy dose reduction. We defined primary G-CSF prophylaxis as upfront use in the first chemotherapy cycle and continuation in subsequent cycles. The administration of G-CSF after an episode of FN during a previous chemotherapy cycle was considered secondary use; patients who received such treatment were excluded from the analysis, as indicated in the Patient selection subsection. Antibiotic treatment was administered to patients who showed grade 3 or 4 neutropenia at nadir.[13] Neupogen (filgrastim) 30 MU was the form of G-CSF used during the study period; this treatment was administered subcutaneously from day 4 to day 7 of each chemotherapy cycle.

Febrile neutropenia and other adverse events

Febrile neutropenia was defined as a single reading of oral temperature ≥38.3°C or a sustained (≥1 h) oral temperature of ≥38.0°C, with either an ANC of <0.5 × 10^9 cells/L or an ANC of <1.0 × 10^9 cells/L and predicted decrease to <0.5 × 10^9 cells/L over the next 48 hours.[14] Haematological and other non-haematological adverse events were categorised and graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0); they were expressed as maximum toxicity per patient. Other adverse effects were reported as grade 3 or 4.

Hospital admission for chemotherapy-related toxicities

An admission was regarded as a single hospital admission that occurred between two consecutive chemotherapy cycles; admissions were recorded until 1 month after the final cycle of chemotherapy. If neutropenic fever was diagnosed or suspected, patients were admitted for isolation, sepsis tests, and antibiotic treatment; if patients refused admission, they were prescribed oral antibiotics. If indicated, patients were also admitted for treatment of chemotherapy-related adverse effects. Admissions were categorised according to the primary diagnosis at the time of admission.

Statistical analyses

Descriptive statistics were used to summarise

TABLE 1. Characteristics of patients with breast cancer, stratified according to primary granulocyte-colony stimulating factor prophylaxis status*

	Non-G-CSF (n=38)	Primary G-CSF (n=193)	P value
Age at diagnosis, y	49.8 ± 8.9	52.1 ± 9.9	0.183
Body weight, kg	57.9 ± 8.3	57.8 ± 9.0	0.971
Body height, cm	155.3 ± 4.7	156.2 ± 6.0	0.395
Body mass index, kg/m^2	24.0 ± 3.4	23.7 ± 3.6	0.440
<18.5	1 (2.6%)	7 (3.6%)	0.953
18.5-23.9	21 (55.3%)	105 (54.4%)	
≥24.0	16 (42.1%)	81 (42.0%)	
Menopausal status			0.704
Premenopausal	19 (50.0%)	103 (53.4%)	
Postmenopausal	19 (50.0%)	90 (46.6%)	
Current smoker	1 (2.6%)	2 (1.0%)	0.068
Current drinker	0	2 (1.0%)	0.222
No. of co-morbidities			0.268
0	19 (50.0%)	101 (52.3%)	
1	15 (39.5%)	55 (28.5%)	
≥2	4 (10.5%)	37 (19.2%)	
Tumour-related factors			
Clinical stage			0.534
Early	35 (92.1%)	175 (90.7%)	
Locally advanced	3 (7.9%)	18 (9.3%)	
Histology			0.527
Invasive ductal carcinoma	34 (89.5%)	178 (92.2%)	
Others	4 (10.5%)	15 (7.8%)	
Breast cancer cell differentiation			0.465
Well	2 (5.3%)	21 (10.9%)	
Moderate	12 (31.6%)	67 (34.7%)	
Poor	21 (55.3%)	98 (50.8%)	
Unknown	3 (7.9%)	7 (3.6%)	
LVI			0.455
Negative	25 (65.8%)	120 (62.2%)	
Positive	9 (23.7%)	61 (31.6%)	
Unknown	4 (10.5%)	12 (6.2%)	
Molecular biomarkers			
ER-positive	24 (63.2%)	113 (58.5%)	0.547
PR-positive	17 (44.7%)	90 (46.6%)	0.905
HER2-positive	9 (23.7%)	60 (31.1%)	0.385
Triple-negative	10 (26.3%)	46 (23.8%)	0.770
Ki67			0.835
<14	2 (5.3%)	14 (7.3%)	
≥14	12 (31.6%)	66 (34.2%)	
Unknown	24 (63.2%)	113 (58.5%)	

Abbreviations: ER = oestrogen receptor; G-CSF = granulocyte-colony stimulating factor; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; non-G-CSF = patients who did not receive primary G-CSF prophylaxis; primary G-CSF = patients who received primary G-CSF prophylaxis; PR = progesterone receptor

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

baseline patient and tumour characteristics, chemotherapy delivery, and adverse events. The Chi squared test (or Fisher's exact test) and Student's *t* test (or Mann–Whitney *U* test) were used for comparisons of categorical and continuous variables, respectively. Multivariate logistic regression models were used to calculate the relative risk and 95% confidence interval for the occurrence of FN with primary G-CSF prophylaxis after adjustment for age.

The total percentage of planned doses received was calculated as the sum of the percentage of planned doses over four cycles divided by the number of cycles of chemotherapy administered. Dose intensity was calculated as the cumulative dose (mg/m^2) divided by the total duration of chemotherapy (wk). Planned dose intensity was calculated as the planned cumulative dose (mg/m^2) divided by the planned treatment duration (wk). Relative dose intensity was calculated as the ratio of delivered dose intensity to planned dose intensity. Chemotherapy dose delay was defined as a delay of ≥3 days from the planned treatment date. In all statistical analyses, P<0.05 was considered indicative of statistical significance. All data analyses were performed using SPSS software (Windows version 26.0; IBM Corp, Armonk [NY], United States).

Results

Baseline characteristics of patients according to primary granulocyte-colony stimulating factor prophylaxis status

During the initial review, 261 patients were identified and eight of them presented with synchronous bilateral breast cancer. In total, 30 patients were excluded from analysis for the following reasons: previous receipt of chemotherapy (n=2), mixed TC and doxorubicin plus cyclophosphamide or other chemotherapy regimens (eg, epirubicin plus cyclophosphamide, or cyclophosphamide plus methotrexate plus 5-fluorouracil) [n=14], or more than four cycles of TC (n=6); failure to complete four cycles of chemotherapy (n=3; 1 died of pneumonia, 1 discontinued chemotherapy after one cycle because of advanced age, and 1 discontinued chemotherapy after three cycles for unspecified reasons); and use of G-CSF after the occurrence of FN (n=5). Finally, 231 female Chinese patients with breast cancer were included in this study; 193 patients (83.5%) received primary G-CSF prophylaxis (Table 1). Age at diagnosis, body weight and height, body mass index, and menopausal and co-morbidity statuses were comparable between patients with and without primary G-CSF prophylaxis. The distributions of tumour stages, histological subtypes, histological grades, and molecular biomarker statuses were also similar between the two groups.

Development of febrile neutropenia and other chemotherapy-related toxicities

In total, 106 patients (45.9%) had ≥1 episode of neutropenia; 69 patients (65.1%) developed grade 3 or 4 neutropenia (Table 2). Among patients with neutropenia, the incidences of FN were 40.0% (12/30) in the non-G-CSF group and 36.8% (28/76) in the G-CSF group. Compared with patients who did not receive G-CSF prophylaxis, primary G-CSF prophylaxis was associated with a lower incidence of FN (31.6% vs 14.5%) and a lower incidence of grade 3 or 4 neutropenia (57.9% vs 24.7%) [Table 2]; the relative risks were 0.45 (95% confidence interval=0.25-0.81) and 0.43 (95% confidence interval=0.30-0.62), respectively. However, G-CSF prophylaxis was not associated with reduced incidences of non-neutropenic fever and infection. The incidences of grade 3 or 4 chemotherapy-related toxicities other than neutropenia were very low among our patients. Only four episodes of grade 3 or 4 chemotherapy-related adverse events were observed (one episode of anaemia, one episode of non-neutropenic leukopenia, and two episodes of diarrhoea).

Delivery of chemotherapy

Primary G-CSF prophylaxis helped to maintain the planned regimen of TC chemotherapy (Table 3).

TABLE 2. Incidences of chemotherapy-related toxicities during docetaxel plus cyclophosphamide chemotherapy in patients with breast cancer, stratified according to primary granulocyte-colony stimulating factor prophylaxis status*

	Non-G-CSF (n=38)	Primary G-CSF (n=193)	Crude RR (95% CI)	Adjusted RR† (95% CI)
Neutropenia in ≥1 cycle	30 (78.9%)	76 (40.0%)	0.57 (0.40-0.64)	0.51 (0.40-0.65)
Grade 3 or 4 neutropenia in ≥1 cycle	22 (57.9%)	47 (24.7%)	0.43 (0.30-0.62)	0.43 (0.30-0.62)
Febrile neutropenia in ≥1 cycle	12 (31.6%)	28 (14.5%)	0.46 (0.26-0.82)	0.45 (0.25-0.81)
Fever without neutropenia	4 (10.5%)	46 (23.8%)	2.26 (0.87-5.92)	2.08 (0.80-5.42)
Infection in ≥1 cycle of chemotherapy	2 (5.3%)	23 (11.9%)	2.26 (0.56-9.20)	2.33 (0.57-9.46)

Abbreviation:s CI = confidence interval; G-CSF = granulocyte-colony stimulating factor; non-G-CSF = patients who did not receive primary G-CSF prophylaxis; primary G-CSF = patients who received primary G-CSF prophylaxis; RR = relative risk

* Data are shown as No. (%), unless otherwise specified

† Adjusted for age

TABLE 3. Delivery of docetaxel plus cyclophosphamide chemotherapy to patients with breast cancer, stratified according to primary granulocyte-colony stimulating factor prophylaxis status*

	Non-G-CSF (n=38)	Primary G-CSF (n=193)	P value
Dose reduction in any cycle			0.048
None	24 (63.2%)	144 (74.6%)	
During T only	1 (2.6%)	15 (7.8%)	
During both T and C	13 (34.2%)	34 (17.6%)	
Overall percentage of scheduled T dose received (%), median (range)	100.0 (77.5-100.0)	100.0 (80.0-100.0)	0.079
100	24 (63.2%)	144 (74.6%)	0.326
90-99	7 (18.4%)	22 (11.4%)	
<90	7 (18.4%)	27 (14.0%)	
Overall percentage of scheduled C dose received (%), median (range)	100.0 (81.3-100.0)	100.0 (81.3-100.0)	0.011
100	25 (65.8%)	159 (82.4%)	0.066
90-99	8 (21.1%)	20 (10.4%)	
<90	5 (13.2%)	14 (7.3%)	
Cycle delay (≥3 d)	10 (26.3%)	109 (56.5%)	0.001

Abbreviation:s C = cyclophosphamide; G-CSF = granulocyte-colony stimulating factor; non-G-CSF = patients who did not receive primary G-CSF prophylaxis; primary G-CSF = patients who received primary G-CSF prophylaxis; T = docetaxel

* Data are shown as No. (%), unless otherwise specified

TABLE 4. Hospital admissions among patients with breast cancer, stratified according to primary granulocyte-colony stimulating factor prophylaxis status*

	Non-G-CSF (n=38)	Primary G-CSF (n=193)	P value
≥1 Admission			0.095
No	24 (63.2%)	147 (76.2%)	
Yes	14 (36.8%)	46 (23.8%)	
No. of admissions			0.033
1	13 (34.2%)	32 (16.6%)	
≥2	1 (2.6%)	14 (7.3%)	
Admission for febrile neutropenia	12 (31.6%)	24 (12.4%)	0.02

Abbreviation:s G-CSF = granulocyte-colony stimulating factor; non-G-CSF = patients who did not receive primary G-CSF prophylaxis; primary G-CSF = patients who received primary G-CSF prophylaxis

* Data are shown as No. (%), unless otherwise specified

When compared with the non-G-CSF group, the proportion of patients who received the standard dose of TC was higher among patients in the G-CSF group (63.2% vs 74.6%); moreover, the proportion of patients with an overall dose deduction of >10% for docetaxel or cyclophosphamide was lower among patients in the G-CSF group (18.4% vs 14.0% and 13.2% vs 7.3%, respectively), although the difference was not statistically significant. However, compared with the non-G-CSF group, more patients in the G-CSF group experienced chemotherapy cycle delays (26.3% vs 56.5%). There were no significant differences in dose intensity or relative dose intensity for both docetaxel and cyclophosphamide between the G-CSF and non-G-CSF group (online supplementary Table 1).

Rate of hospital admission

Sixty patients had ≥1 hospital admission for a severe chemotherapy-related adverse event; 36 of these patients (60%) were diagnosed with FN. Compared with the non-G-CSF group, the hospital admission rate was lower in the primary G-CSF prophylaxis group, particularly in terms of admission for FN (31.6% vs 12.4%) [Table 4].

Discussion

Primary granulocyte-colony stimulating factor prophylaxis reduced febrile neutropenia and severe neutropenia

To our knowledge, this is the first study to demonstrate an association between the use of a fixed schedule of G-CSF prophylaxis (days 4 to 7) and the reduction of neutropenia and FN incidences in patients with early-stage breast cancer who received adjuvant TC chemotherapy. Our study demonstrated that patients who received primary G-CSF prophylaxis were significantly more likely to maintain their planned regimen of chemotherapy and have a lower rate of hospital admission. These findings suggest that G-CSF prophylaxis can enhance treatment efficacy and conserve medical resources.

Chinese patients on docetaxel-based chemotherapy had higher incidences of neutropenia/febrile neutropenia

Our results are consistent with previous reports that the FN rate was higher among patients receiving TC chemotherapy in the absence of G-CSF.[3,15-17] Rates of myelosuppression and neutropenia during docetaxel-based chemotherapy were higher in our Chinese patients compared with those in Caucasian patients in previous studies.[18-20] In the original TC study, incidence of FN was only 5%.[3] Inter-individual and inter-ethnic variations in pharmacokinetics and pharmacodynamics may be linked to variations in docetaxel toxicity.[21-23]

Four-day course of granulocyte-colony stimulating factor prophylaxis was effective

With regard to the schedule of G-CSF prophylaxis, international guidelines recommend initiation between 24 and 72 hours after the last day of chemotherapy, with continuation until sufficient and stable ANC recovery has been achieved after nadir.[5,10,11] The optimal clinical benefits of filgrastim have been achieved with approximately 11 daily injections; ANC recovery typically requires 10 to 11 days.[5] Therefore, the median recommended duration of daily filgrastim injections is 10 to 11 days.[5,11] Nevertheless, the chemotherapy schedule varies in clinical practice.[5,24,25] In a previous study, von Minckwitz et al[8] found that daily G-CSF was most frequently administered at five to seven doses per cycle. We initiated G-CSF on day 4 in accordance with the recommendation (mentioned above) that G-CSF should be initiated between 24 and 72 hours after chemotherapy. According to the docetaxel prescribing information, a median of 7 days is needed to reach nadir; the median duration to reach severe neutropenia (<500 cells/mL) is also 7 days. Based on our previous experience concerning nadir, we examined complete blood counts from day 7 to day 11; we observed that the duration of neutrophil nadir for docetaxel was short and the ANC rapidly rebounded after day 10. Because the median neutrophil nadir of docetaxel typically occurs on day 7, the administration of G-CSF until day 7 would constitute the shortest duration of G-CSF injection; the increased neutrophil count as a result of G-CSF injection (due to the effect of G-CSF) would presumably have a protective effect during the expected neutrophil nadir period.

In this study, FN occurred after the first

cycle in 28 of 193 (14.5%) patients who received primary G-CSF prophylaxis; all of those patients received G-CSF on days 4 to 7. It is important to consider whether this finding suggests that our G-CSF schedule was insufficient for FN prevention. Notably, there have been reports that the initial episode of neutropenia most frequently occurred during the first cycle in patients receiving cancer chemotherapy.[6,25,26] The lower apparent risk after the first cycle presumably results from subsequent dose reductions and delays, or from the secondary use of a white blood cell growth factor.[6,27] The high frequency of first-cycle FN has been proposed to emphasise the need for early (during the first cycle) initiation of G-CSF to reduce the risk of FN. A longer duration of G-CSF prophylaxis may further reduce the incidence of first-cycle FN, but this hypothesis requires further investigation.

Granulocyte-colony stimulating factor prophylaxis enabled adequate chemotherapy dose delivery

We found that primary G-CSF prophylaxis influenced the incidences of FN and FN-related hospitalisation and also enabled adequate chemotherapy dose delivery. Our findings were similar to the results reported by von Minckwitz et al[8]; however, their study involved a comparison of primary prophylaxis with long-acting pegfilgrastim to either no G-CSF treatment or any cycle of G-CSF/pegfilgrastim. In the group of patients who received G-CSF, the longer duration of chemotherapy might have offset the effect of the higher total percentage of scheduled chemotherapy doses on dose intensity and relative dose intensity. These findings were analogous to the findings in a Cochrane review, which showed CSF treatment did not help much in maintaining the planned chemotherapy schedules.[9] Additionally, von Minckwitz et al[8] reported that neutropenia prophylaxis influenced chemotherapy dose reductions (≥15%) but did not affect the incidence of chemotherapy dose delays (≥3 days). Similarly, in a study that evaluated the effect of pegfilgrastim during the first and subsequent cycles versus placebo, the proportion of patients who received their planned dose on time (defined as receiving ≥80% of the planned dose and no dose ≥3 days late) did not significantly differ between the two groups. The authors of the study concluded that no difference had been present because patients who developed FN were allowed to receive pegfilgrastim in subsequent cycles, which (because of study design) prevented the identification of a difference between the pegfilgrastim and placebo groups.[26]

Although the reduction of FN incidence is an important clinical outcome, G-CSF prophylaxis might facilitate the maintenance of chemotherapy dose intensity[7]; G-CSF has also been used as an adjunct to achieve moderate increases in dose intensity. Early clinical trials of patients with solid malignancies demonstrated a limited survival benefit for patients who received higher dose therapy.[28] In clinical studies, dose-dense schedules (ie, with shortened treatment intervals) have shown increased survival, whereas the benefit in dose escalation studies has been less consistent.[6] Notably, a meta-analysis showed that the receipt of primary G-CSF prophylaxis was associated with a modest reduction in all-cause mortality, compared with the absence of primary prophylaxis.[29] Recently published meta-analyses confirm the survival benefit of dose-dense chemotherapy.[29,30] These provide supporting evidence that ensuring chemotherapy dose intensity is an important consideration for treatment outcome which is particularly relevant in adjuvant chemotherapy settings. Further studies are awaited to assess the effects of chemotherapy dose delivery on survival outcomes in our patients with early breast cancer.

Our results showed that G-CSF prophylaxis reduced the rate of hospital admission for FN. Conventional management of FN involves hospital admission with intravenous administration of broad-spectrum antibiotics for 5 to 7 days. The mean length of hospitalisation for FN may exceed 1 week; patients must be placed in isolation rooms to undergo numerous diagnostic procedures and receive intravenous antibiotic support, and there is a need to consider the potential complications of such therapy (American Society of Clinical Oncology guideline 1994, 2000).[31] The benefit of reducing the rate of hospital admission is that it can reduce demands on the resources of a public healthcare system with a limited number of in-patient beds. Additionally, the reduced rate of hospital admission can help to minimise disruption for patients and their families, thereby avoiding negative impacts on quality of life.

Study implications

The patients in this study received treatment from November 2007 to October 2013. Among the patients, 14.7% had luminal A–like breast cancer subtypes according to histopathological criteria (online supplementary Table 2); thus far, patients with such breast cancer subtypes have experienced minimal benefits from chemotherapy. With the increasing use of gene expression profiling as a personalised medicine approach for adjuvant chemotherapy in patients with hormone receptor–positive, HER2-negative breast cancers, the use of adjuvant chemotherapy has become increasingly selective for such patients; nevertheless, it remains important for patients with HER2-positive and

triple-negative breast cancers. The TC regimen is an important type of adjuvant chemotherapy; it is recommended within the National Comprehensive Cancer Network guidelines. Because it is an anthracycline-free regimen, TC chemotherapy has been compared with anthracycline-containing regimens in some large, randomised trials; it has demonstrated excellent results.[32,33] The TC regimen is considered an efficacious and less-toxic option in lower-risk patients, as well as patients with known cardiac disease or pre-existing risk factors for cardiac toxicity.[32,33] Routine G-CSF prophylaxis has made adjuvant TC chemotherapy safer and more successful. Currently, the 4-day G-CSF schedule is widely used for patients in our hospital who receive other docetaxel-containing regimens, such as TCH (ie, trastuzumab, carboplatin, and docetaxel) and docetaxel 100 mg/m^2 regimens; the outcomes are generally positive.

Study limitations

First, this study used a retrospective cohort design and only included patients from a single centre. Thus, the overall sample size was moderate and the non-G-CSF group included a small number of patients. Moreover, because this was an observational study without randomisation, the number of patients who received G-CSF prophylaxis substantially differed from the number of patients who did not receive such prophylaxis. Our results require confirm in multicentre studies with diverse patient populations. Second, indication bias might have been present, such that patients who received G-CSF might constitute a distinct group, compared with patients who did not receive G-CSF. We suggested the use of primary G-CSF prophylaxis to each patient who was scheduled to receive adjuvant TC chemotherapy; most patients accepted this suggestion (193/231). Among 43 patients who did not receive G-CSF treatment at the first cycle of chemotherapy, only five received secondary administration of G-CSF, which indicated that cost was the main factor influencing receipt of primary G-CSF prophylaxis. Nevertheless, we used multivariate logistic regression models to adjust for potential confounding factors (eg, baseline differences between the two groups). Third, incomplete documentation of adverse effects might have influenced our findings because only significant adverse effects were recorded for most study participants. Febrile neutropenia and hospital admission were the major clinical outcomes recorded in medical records; therefore, medication-related adverse effects might have been neglected. Finally, because only short-term toxicity (ie, neutropenic toxicity) was examined in this study, the long-term effects of chemotherapy (eg, neurotoxicity) and G-CSF prophylaxis on quality of life should be addressed in future studies.

Conclusion

Our study demonstrated that the use of 4-day primary G-CSF prophylaxis can reduce neutropenic toxicity from adjuvant TC chemotherapy; it enables successful chemotherapy treatment and facilitates adequate chemotherapy dose delivery. Further studies are needed to assess the effects of primary G-CSF prophylaxis and chemotherapy dose delivery on survival outcomes in patients with breast cancer.

Author contributions

Concept or design: CCH Kwok, F Wang, SLA Tse.
Acquisition of data: CCH Kwok, SPY Wong.
Analysis or interpretation of data: WH Wong, CCH Kwok, SLA Tse, F Wang, LL Chan.
Drafting of the manuscript: CCH Kwok.
Critical revision of the manuscript for important intellectual content: CCH Kwok, F Wang, SLA Tse, MCS Wong.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As the Editor-in-Chief and adviser of the journal, respectively, MCS Wong and SLA Tse were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Ethics approval

This study was approved by the Hong Kong Hospital Authority Kowloon West Cluster Research Ethics Committee (Ref: KW/EX-12-068 [53-03]). The requirement for informed consent was waived.

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