Neutrophil Recovery in Breast Cancer Patients Receiving Docetaxel-Containing Chemotherapy with and without Granulocyte Colony-Stimulating Factor Prophylaxis

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Keywords

Breast cancer · Granulocyte colony-stimulating factor prophylaxis · Neutrophil · Chemotherapy

Abstract

Objective: The primary outcome of the current study is, whether there is a protective effect of prior chemotherapy or of prior granulocyte colony-stimulating factor (G-CSF) on the next cycle blood cell counts. **Methods:** Hematologic toxicity was evaluated, based on a randomized phase III study in breast cancer patients ($n = 167$) with $>20\%$ risk of febrile neutropenia. The primary endpoint was the nadir blood cell counts for patients treated with G-CSF given during all 6 chemotherapy cycles or limited to the first 2 chemotherapy cycles only. **Results:** For the present analyses, 47 patients were eligible. In the G-CSF 1–6 arm, the median white blood cell count (WBC) and absolute neutrophil count (ANC) nadir slowly decreased from $10.8 \times 10^9/L$ in cycle 1 to $7.5 \times 10^9/L$

in cycle 6 and from $7.1 \times 10^9/L$ to $5.5 \times 10^9/L$, respectively. The median WBC nadir in the G-CSF 1–2 arm decreased from $1.2 \times 10^9/L$ in cycle 3 to $0.9 \times 10^9/L$ in cycle 6 and the ANC nadir showed a grade 4 neutropenia of $0.1 \times 10^9/L$ in cycles 3–6. All patients had ANC recovery to normal levels ($\geq 1.5 \times 10^9/L$) without delay on day 1 of the next cycle. **Conclusion:** We conclude that there is no protective effect of prior G-CSF or prior chemotherapy use on nadir blood cell counts in subsequent cycles.

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Introduction

An anthracycline-taxane chemotherapy regime is effective in breast cancer, but it is also very myelotoxic with a substantial risk of febrile neutropenia (FN) [1, 2]. The FN incidence of myelosuppressive chemotherapy regimes without primary granulocyte colony-stimulating

factor (G-CSF) prophylaxis is reported to be highest in the first (2) chemotherapy cycles, with declining incidence thereafter [1–4].

One might hypothesize that chemotherapy-induced myelosuppression leads to intrinsic hematopoietic growth factor production and as such protects against FN during later chemotherapy cycles. However, so far no relevant articles regarding this subject have been published.

At the same time, for patients who are treated with primary G-CSF prophylaxis (i.e., from the first cycle onwards), one may conclude that continuation of prophylaxis during later chemotherapy cycles may be less effective because of the lower baseline risk of FN in later chemotherapy cycles [1, 2]. Therefore, we performed a phase III study in which breast cancer patients treated with myelosuppressive chemotherapy were randomized to G-CSF prophylaxis during all 6 chemotherapy cycles or to G-CSF prophylaxis limited to the first 2 chemotherapy cycles only [5]. In contrast to what we had expected, G-CSF use limited to the first 2 chemotherapy cycles was not effective, as in total 36% of patients developed FN compared to 10% in the control arm. Interestingly, we observed that the highest FN incidence in the experimental arm occurred in the third chemotherapy cycle (24% of patients), which was the first cycle without G-CSF prophylaxis. Remarkably, in the fourth to sixth chemotherapy cycle, the incidence of FN again declined to an average of 5%. This might possibly have been the result of secondary antibiotic prophylaxis (7% of patients), secondary G-CSF prophylaxis (17% of patients) or chemotherapy dose modifications (8% of patients).

However, this observation may also be explained by a protective effect of prior chemotherapy or of prior G-CSF on the blood cell counts of the fourth to second chemotherapy cycle. If indeed this is the case, blood cell counts would gradually increase during subsequent chemotherapy cycles. We, therefore, studied nadir blood cell counts over the subsequent chemotherapy cycles in patients treated in the above-mentioned phase III clinical trial. To prevent confounding, we excluded from our present analysis patients who developed FN event, received secondary G-CSF prophylaxis or chemotherapy dose reductions during later cycles.

Methods

Clinical Phase III Study

Full methods and results of the phase III study have been published before [5, 6]. Patients were randomized to G-CSF prophylaxis during all 6 chemotherapy cycles or to G-CSF prophylaxis

limited to the first 2 chemotherapy cycles only. For the phase III study, breast cancer patients were eligible if treated with 3-weekly chemotherapy and being at risk of FN according to international guidelines. For example, TAC (docetaxel, Adriamycin, cyclophosphamide) or AT (Adriamycin, docetaxel) are chemotherapy regimens with more than 20% risk of FN; TC (docetaxel, cyclophosphamide) or docetaxel monotherapy have a 10–20% risk of FN and in the presence of one or more patient risk factors, risk of FN increases to more than 20%. Patients were required to have an absolute neutrophil count (ANC) $>1.5 \times 10^9/L$, adequate renal and hepatic function, no signs of an active uncontrolled infection or other serious comorbidity before enrolment.

Study Design

We included the data from patients treated according to the aforementioned phase III study, and evaluated the hematologic nadir toxicity for all included patients per treatment arm.

Subsequently, we selected a subgroup of patients, in whom nadir blood cell counts throughout subsequent chemotherapy cycles were affected by a constant chemotherapy and G-CSF use. Hence, we excluded patients who developed FN, had chemotherapy dose reductions or chemotherapy delays (more than 3 days from scheduled treatment) during treatment or who did not use G-CSF prophylaxis according to plan (either prematurely ceased G-CSF prophylaxis despite randomization to G-CSF prophylaxis during all 6 chemotherapy cycles, “G-CSF 1–6 arm”, or who had secondary G-CSF prophylaxis during cycles 3–6 in the “G-CSF 1–2 arm” because of FN or other reasons). In case of missing values in cycles 4–6, patients were considered not assessable and therefore excluded.

Blood samples were taken on day 1 and nadir blood cell counts on days 10–14 of each cycle to assess myelotoxicity. In case of FN, daily complete blood cell counts were to be performed until recovery of ANC $\geq 0.5 \times 10^9/L$.

Study Endpoints

The hematologic toxicity per cycle per treatment arm was evaluated, which was a prespecified secondary endpoint of the randomized clinical phase III trial [5]. We analyzed nadir white blood cell (WBC), neutrophil and platelet counts in patients treated with primary G-CSF prophylaxis during all chemotherapy cycles and of patients treated with G-CSF prophylaxis during cycles 1 and 2 only.

For the current study, the primary endpoint was the nadir blood cell counts in cycles 1–6 for the selected, eligible patients who received G-CSF prophylaxis in cycles 1–6 and the nadir blood cell counts in cycles 3–6 for the selected, eligible patients who per protocol did not receive G-CSF prophylaxis in cycles 3–6 (only G-CSF in cycles 1–2).

All analyses are descriptive in nature.

Results

Patients

In the clinical phase III trial, in total 167 patients were included. For the present research question, 32 patients in the G-CSF 1–6 arm were eligible and 15 patients in the

Fig. 1. CONSORT flow diagram.

G-CSF 1–2 arm. We excluded patients because of FN (8 and 30 patients, respectively), because of chemotherapy delay or dose reductions (11 and 7, respectively) and because of G-CSF protocol violations (2 and 17, respectively). Other patients were excluded due to missing blood nadir values in one or more cycles (Fig. 1). Baseline characteristics are shown in Table 1.

Nadir Blood Cell Counts

In Table 2, it is shown that in the selected, eligible patients treated in the G-CSF 1–6 arm ($n = 32$), median nadir WBC decreased from $10.8 \times 10^9/L$ in cycle 1 to $7.5 \times 10^9/L$ in cycle 6 and ANC from $7.1 \times 10^9/L$ to $5.5 \times 10^9/L$. Similarly, nadir blood cell counts decreased during treatment in the G-CSF 1–2 arm when primary G-CSF prophylaxis was discontinued according to study protocol in cycle 3 and further: nadir WBC dropped from $1.2 \times 10^9/L$ to $0.9 \times 10^9/L$ and nadir ANC showed a persistent grade 4 neutropenia of $0.1 \times 10^9/L$ in cycles 3–6 (Table 3).

Of note, when considering the total patient population irrespective of changes in chemotherapy or G-CSF administration, nadir blood cell counts in the G-CSF 1–6 arm gradually *decreased* during treatment, whereas in the G-CSF 1–2 arm nadir blood cell counts gradually *increased* from cycle 3 to 6: from $1.2 \times 10^9/L$ to $1.8 \times 10^9/L$ for WBC and from $0.1 \times 10^9/L$ to $0.5 \times 10^9/L$ for ANC (Tables 2, 3).

Nadir platelet counts remained stable over the consecutive chemotherapy cycles (data not shown).

Day 1 Blood Cell Counts

In patients in the G-CSF 1–6 arm who used G-CSF prophylaxis during all chemotherapy cycles, the day 1 ANC values remained stable throughout cycles 3–6. The median day 1 ANC values were on average $5.8 \times 10^9/L$. In contrast, in the G-CSF 1–2 arm without secondary G-CSF prophylaxis in cycles 3–6 as defined in the study protocol the median day 1 ANC slowly declined from cycle 3 to 6 (data not shown).

Table 1. Baseline characteristics

	G-CSF 1–6 (n = 84)	G-CSF 1–6 (n = 32)	G-CSF 1–2 (n = 83)	G-CSF 1–2 (n = 15)
Patient characteristics				
Age, years	50 (26–69)	56 (32–73)	50 (31–70)	58 (39–76)
≤65 years	79 (94)	30 (94)	78 (94)	13 (87)
ECOG PS 0–1	81 (96)	32 (100)	81 (98)	15 (100)
(Neo-)adjuvant treatment setting	84 (100)	32 (100)	80 (96)	14 (93)
Primary antibiotics prophylaxis	34 (40)	17 (53)	36 (43)	5 (33)
Baseline blood counts				
White blood cell count ($\times 10^9/L$)	7.7 (3.4–21.1)	7.0 (4–19.6)	7.6 (4.3–18.0)	6.8 (4.3–11.7)
Absolute neutrophil count ($\times 10^9/L$)	4.8 (2.0–64.3)	4.4 (2.1–17.8)	4.5 (2.1–16.2)	3.9 (2.6–8.4)
Platelet count ($\times 10^9/L$)	296 (129–541)	297 (143–541)	289 (160–544)	262 (160–544)
Chemotherapy				
TAC	81 (96)	32 (100)	77 (93)	14 (93)
FEC-D	3 (4)	0 (0)	3 (4)	0 (0)
DOC	0 (0)	0 (0)	2 (2)	1 (7)
TC	0 (0)	0 (0)	1 (1)	0 (0)

Figures indicate median (range) or *n* (%). G-CSF, granulocyte colony-stimulating factor; PS, performance score; TAC, docetaxel, doxorubicin, cyclophosphamide; FEC-D, 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel; DOC, docetaxel; TC, docetaxel, cyclophosphamide.

Table 2. Hematologic toxicity of the G-CSF 1–6 arm in all patients and subgroup^a: nadir values

	G-CSF 1–6 (n = 84)		G-CSF 1–6 (n = 32)	
	median	IQR	median	IQR
<i>White blood cell count</i> ($\times 10^9/L$)				
Cycle 1	10.3	6.2–13.6	10.8	5.5–15.2
Cycle 2	10.1	8.1–12.3	10.1	7.9–15.4
Cycle 3	9.1	7.2–11.8	10.1	7.4–15.4
Cycle 4	9.1	7.4–11.8	9.4	5.1–12.0
Cycle 5	8.9	6.4–10.7	8.9	5.4–11.8
Cycle 6	7.8	5.3–9.3	7.5	3.4–9.5
<i>Neutrophil count</i> ($\times 10^9/L$)				
Cycle 1	7.1	3.9–9.5	7.1	3.9–10.9
Cycle 2	6.7	5.3–8.6	7.5	5.7–11.0
Cycle 3	6.6	4.8–8.8	7.4	4.8–12.3
Cycle 4	6.6	5.2–8.4	7.0	3.4–9.6
Cycle 5	6.5	3.8–8.0	6.7	3.5–8.8
Cycle 6	5.3	3.3–6.8	5.5	2.5–7.4

G-CSF, granulocyte colony-stimulating factor; IQR, interquartile range. ^a Subgroup, patients without febrile neutropenia, chemotherapy dose reductions or delay, G-CSF prophylaxis “violation” or missing values in cycles 3–6.

Discussion

FN is a serious side effect of cancer treatment [3, 4]. For patients at risk (>20%) of FN, primary G-CSF prophylaxis is recommended as it reduces the risk of chemotherapy-induced FN [7].

Previously, the risk of FN was presumed to be highest during the first chemotherapy cycles, but we showed that discontinuation of G-CSF prophylaxis after the first 2 chemotherapy cycles resulted in a rebound high FN incidence in the next chemotherapy cycles [5]. Apparently, a prior chemotherapy cycle in combination with G-CSF prophylaxis seemed not to be myeloprotective for a later chemotherapy cycle. In order to find support for this latter assumption, we looked more in detail to the hematologic toxicity in patients in whom in-patient comparisons were possible, e.g., patients without chemotherapy dose modifications or changes in G-CSF prophylaxis during their treatment and without FN event. In our explorative analyses, we show that the median nadir WBC and ANC slowly decreased while continuing on G-CSF prophylaxis, and that the median ANC nadir remained steadily low in cycles 3–6 in those who did not receive G-CSF prophylaxis during these cycles. Hence, we conclude that prior G-CSF prophylaxis with pegfilgrastim during 3-weekly chemotherapy and prior chemotherapy have

Table 3. Hematologic toxicity of the G-CSF 1–2 arm in all patients and subgroup^a: nadir values

	G-CSF 1–2 (<i>n</i> = 83)		G-CSF 1–2 (<i>n</i> = 15)	
	median	IQR	median	IQR
<i>White blood cell count</i> ($\times 10^9/L$)				
Cycle 3	1.2	0.7–1.8	1.2	0.8–1.4
Cycle 4	1.5	0.9–5.1	1.0	0.8–1.5
Cycle 5	1.4	1.0–6.3	1.2	0.8–1.4
Cycle 6	1.8	0.9–5.9	0.9	0.7–1.8
<i>Neutrophil count</i> ($\times 10^9/L$)				
Cycle 3	0.1	0–0.5	0.1	0–0.2
Cycle 4	0.2	0.1–3.6	0.1	0–0.1
Cycle 5	0.2	0.1–4.3	0.1	0.03–0.1
Cycle 6	0.5	0.1–4.0	0.1	0.05–0.5

G-CSF, granulocyte colony-stimulating factor; IQR, interquartile range. ^a Subgroup, patients without febrile neutropenia, chemotherapy dose reductions or delay, G-CSF prophylaxis “violation” or missing values in cycles 3–6. ^b

no myeloprotective effect on subsequent chemotherapy cycles.

Pegfilgrastim acts by self-regulated, neutrophil-mediated clearance [8]. In a dose-ranging pegfilgrastim study in breast cancer patients, it was demonstrated that the exposure to pegfilgrastim was lower in cycle 3 than in cycle 1; however, the ANC nadir improved and the duration of neutropenia decreased in cycle 2 and the subsequent cycles, suggesting an expansion of neutrophil and neutrophil precursors mass in the later cycles that results in an increase in drug clearance [9]. This suggestion was supported by Invernizzi et al. [10], who demonstrated not only an increase in ANC (evaluated on day 14 or later and immediately before next chemotherapy) but also an increase in immature myeloid cells in peripheral blood after the first chemotherapy cycle given with G-CSF support with a relatively constant level in the subsequent cycles. Without G-CSF support, no increase in the neutrophil count immediately before chemotherapy occurs; the count was the lowest around 2 weeks after chemotherapy with return to baseline on day 1 of chemotherapy. Also, progenitor cell apoptosis was significantly higher in case no pegfilgrastim support was given compared with pegfilgrastim support [10, 11]. So, an increase in progenitor pool and a decrease in apoptosis could be one factor explaining the differences in blood cell counts between both treatment arms. With this mechanism of action of G-CSF, we would have expected an increase in blood cell

counts in the next chemotherapy cycle; however, we observed a decrease.

The post-nadir ANC of $\geq 1.0 \times 10^9/L$ is of relevance as it is seen as a surrogate marker threshold of pegfilgrastim clearance to subtherapeutic levels [12, 13]. All our patients experienced an ANC recovery to normal levels ($\geq 1.5 \times 10^9/L$) on day 1 of a new cycle while on G-CSF prophylaxis.

Previously, it was reported that the incidence of FN and of grade 4 neutropenia declines during later chemotherapy cycles, and that this cannot entirely be explained by the use of secondary G-CSF prophylaxis or chemotherapy dose reductions [4, 14]. We also noticed a slight increase in nadir WBC and ANC during cycles 3–6 in the G-CSF 1–2 arm, but after exclusion of patients who reinitiated G-CSF prophylaxis (*n* = 17) and of patients who had chemotherapy adjustments (*n* = 7), we saw a persistent steady grade 4 neutropenia. Of note, we did not exclude patients with primary antibiotics prophylaxis as its value in reducing grade 4 neutropenia is neglectable.

Factors that increase risk of neutropenia and FN are patient and treatment related. Patient risk factors are pretreatment, older age, lower weight, vascular comorbidity and baseline low WBC counts, and higher bilirubin levels [15–17]. We could not identify any of these pretreatment patient risk factors in our patient population. Of relevance, the occurrence of FN increases the risk for a new FN event, so we excluded the 38 patients that developed FN to exclude possible confounding. Several covariates in relation with interindividual variation in the time course of neutropenia have been investigated. The most relevant predictors for this interindividual variability were albumin, bilirubin, alkaline phosphatase, lactate dehydrogenase, and aspartate aminotransferase [18, 19]. In our population, no interindividual differences for these predictors were seen. Treatment-related risk factors for neutropenia event are prior chemotherapy and the intensity of chemotherapy [14]. Only 1 patient received prior chemotherapy (FEC; 5-fluorouracil, epirubicin, cyclophosphamide), and almost all patients received TAC (docetaxel, Adriamycin, cyclophosphamide) chemotherapy. The greater the myelosuppressive potential of chemotherapy, the lower the ANC nadir [20], which in turn could enhance intrinsic hematopoietic growth factor production and subsequently protect against chemotherapy-induced neutropenia. Little evidence regarding this subject is published. One study demonstrated that in vivo the chemotherapy increases the GM-CSF (granulocyte-macrophage colony-stimu-

lating factor) hematopoietic growth factor [21]. So, if this is true, we would have expected, after excluding all possible confounders, that chemotherapy itself would increase the blood cell counts in the next cycle. However, no such observation was seen.

A limitation of our study is the small number of eligible patients for this analysis, partly due to the relatively high percentage of missing values. This exploratory analysis will form the basis for further research to draw firm conclusions.

In conclusion, we analyzed in an exploratory way chemotherapy-induced hematologic toxicity after exclusion of possible risk factors of neutropenia. Apart from a protective effect of G-CSF for the cycle where G-CSF was given in, myelotoxicity in the consequent cycle seemed not to improve by prior chemotherapy or prior G-CSF.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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