Abstract # 243

PRIMARY PROPHYLAXIS OF FEBRILE NEUTROPENIA IN FEMALE PATIENTS RECEIVING DOSE-DENSE BIWEEKLY CHEMOTHERAPY IN THE CLINICAL ROUTINE: LONG-ACTING GRANULOCYTE COLONY-STIMULATING FACTORS ARE SAFE AND EFFECTIVE

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INTRODUCTION

Dose-dense biweekly chemotherapy (ddCtx) gains increasing importance in the treatment of breast cancer and other gynecologic neoplasms. In contrast to conventional q3w or q4w protocols ddCtx is associated with a higher risk of severe neutropenia and, consecutively, febrile neutropenia (FN) which forces the obligatory use of granulocyte colony-stimulating factors (G-CSFs) as primary prophylaxis (PP) of FN (FNPP). When used alongside with conventional scheduled Ctx regimens, long acting G-CSFs such as pegfilgrastim (PegFG) and lipegfilgrastim (LipFG) have been shown to be more effective as FNPP compared to daily G-CSFs. However the knowledge about the safety and efficacy of these drugs when used as FNPP in addition to q2w protocols in the clinical routine.

This single institution non-interventional study was initiated to investigate both PegFG and LipFG as FNPP in a real-world population of female patients receiving ddCtx for the treatment of various gynecologic malignancies including primary and metastatic breast cancer.

METHODS

- 54 patients receiving ddCtx were included. Patients characteristics are summarized in Table 1.
- 27 patients received PegFG as FNPP (cohort P), 26 patients were given LipFG (cohort L)
- For both cohorts the following hematological parameters were determined at baseline (BL) and for each subsequent ddCtx cycle (C) up to a number of four (C1-4): leukocytes (white blood cell count, WBC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).
- Hematological side effects related to ddCtx and G-CSF-specific adverse reactions (AR) were scored according to the CTCAE 4.03 scale
- The incidence of hematological side effects related to ddCtx including FN, severe neutropenia (G3-4), and severe lymphocytopenia (G3-4) was regarded as a measure of clinical effectiveness of FNPP using either PegFG or LipFG.
- Differences between PegFG and LipFG in regard to FN, ANC, and ALC were analyzed at BL and for C1-4 separately, by using student´s t-tests.
- Differences between both cohorts regarding in the incidence of both hematological complications and G-CSF-related side effects were analyzed by using the Fisher´s exact tests.
- For all statistical calculations, $p < 0.05$ was regarded to indicate statistical significance.

RESULTS

- The median age was 53.0 and 54.0 in cohort P and L, respectively.
- Both cohorts were fairly well balanced in terms of tumor type, disease stage and pretreatment. Trends favoring cohort L in regard to a higher proportion of patients with breast cancer and a lower percentage of pretreated patients with metastatic disease all lacked statistical significance.
- The hematological parameters analyzed are shown in Figure 1. Baseline values of WBC, ANC, and ALC did not differ between cohort P and L.
- Mean values for WBC, ANC, and ALC [10^9/L] for cohort P vs L were: cycle 1, 5.88 vs 12.67, 4.06 vs 12.57, 1.06 vs 1.70; cycle 2, 6.49 vs 12.34, 3.60 vs 10.03, 1.03 vs 1.37; cycle 3, 4.88 vs 17.10, 3.41 vs 12.37, 0.92 vs 1.55; cycle 4, 4.99 vs 8.65, 3.18 vs 6.91, 1.11 vs 1.15. With a few exceptions (WBC and ANC in C4, and ALC in C2 and C4), these differences favoring LipFG over PegFG were statistically significant (Figure 1).
- The incidence of FN, severe neutropenia (G3-4) and severe lymphocytopenia (G3-4) in C1 was 0.0%, 0.0%, and 8.8% in cohort P and 0%, 0%, and 3.7% in cohort L with all differences lacking statistical significance.
- The incidence of FN, severe neutropenia (G3-4) and severe lymphocytopenia (G3-4) in C1-4 was 2.2%, 5.6%, and 5.6% in cohort P and 0%, 3.2%, and 9.5% in cohort L with none of the observed differences being statistically significant.
- G-CSF-specific adverse reactions > G1 (non-neutropenic fever, chills, fatigue, bone pain) were rare and generally manageable (Table 2). More patients in cohort P suffered from fever, chills and fatigue whereas more patients in cohort L experienced bone pain, leukocytosis > 30 x 109/L and hyperleukocytosis > 60 x 10^9/L. None of the differences observed reached statistical significance

CONCLUSIONS

- Two-cohort non-interventional study, not a controlled randomized trial.
- Both cohorts only fairly well balanced in terms of tumor type, proportion of pretreated patients or those with recurrent/metastatic disease
- Strength: (1) represents a real-world population of patients with various gynecologic malignancies receiving long-acting G-CSFs as FNPP alongside with ddCtx; (2) the first study exclusively focusing on ddCtx including patients treated with LipFG.
- Both long-acting G-CSFs safe and highly effective as primary prophylaxis of FN, severe neutropenia and severe lymphocytopenia associated with ddCtx protocols.
- Higher hematological activity of LipFG compared to that of PegFG.
- Unique finding: higher mean ALC values for LipFG vs PegFG.
- The higher hematological activity of LipFG compared to PegFG did not translate into a significantly higher clinical effectiveness in order to prevent FN, severe neutropenia, and severe lymphocytopenia.
- The higher hematological activity of LipFG vs PegFG was not associated with a higher incidence of severe G-CSF-specific adverse reactions.
- Our results argue in favor that a reduced single dose of LipFG (i. e. 4.5 mg q2w) may be sufficient as FNPP for ddCtx in patients suffering from various female genital tract tumors or breast cancer.

Table 1: Patients´ characteristics

		Cohort P n (%)	Cohort L n (%)	p-value
Total		27 (100)	27 (100)	-
Age (years)	Median Range	53.0 30-78	54.0 39-79	N.S.
Tumor type	Breast Ovarian Others	12 (44.4) 12 (44.4) 3 (11.1)	19 (70.4) 8 (29.6) 1 (3.7)	N.S.
Disease status	Primary Recurrent/metastatic	10 (37.0) 17 (63.0)	13 (48.1) 14 (59.9)	N.S.
Previous chemotherapy	No Yes	10 (37.0) 17 (63.0)	13 (48.1) 14 (51.9)	N.S.

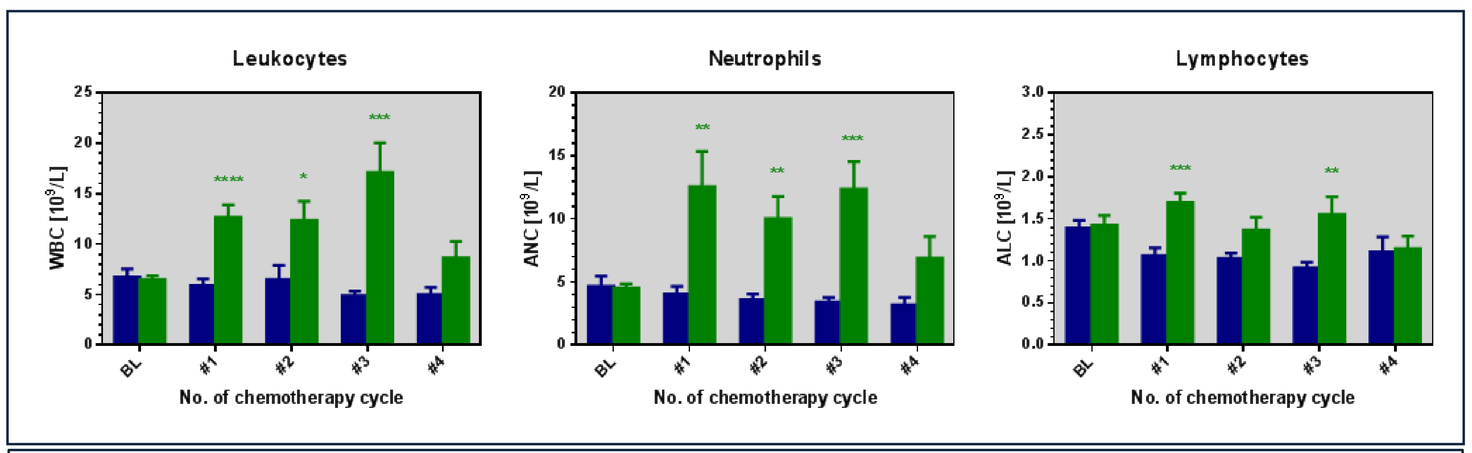

Figure 1: Hematological effectiveness of pegfilgrastim (blue columns) and lipegfilgrastim (green columns). Left, leukocytes; center, neutrophils; right, lymphocytes. Columns show the mean values, error bars represent the SEM. Baseline levels did not differ between cohorts P and L. However, hematological effectiveness was higher for lipegfilgrastim for all three hematopoietic lines investigated

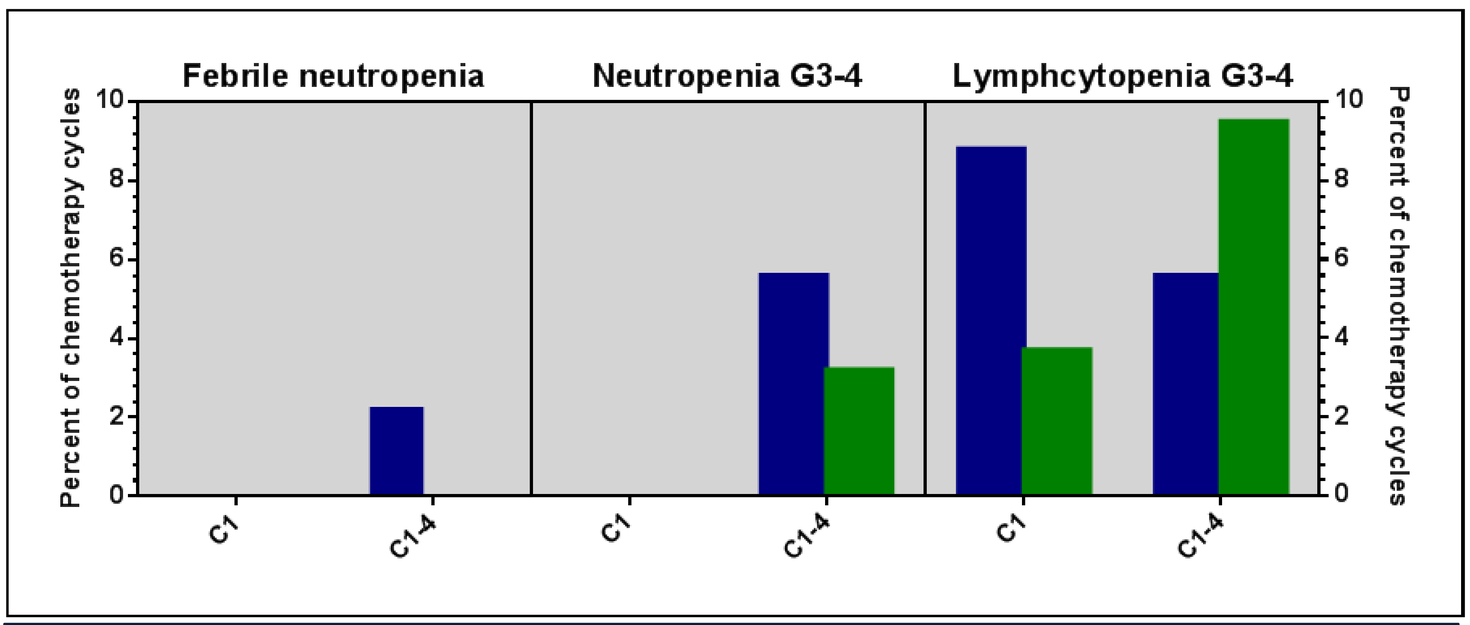

Figure 2: Incidence of febrile neutropenia (left), severe neutropenia (center), and severe lymphocytopenia (right) in dose dense chemotherapy cycles supported by primary prophylaxis with pegfilgrastim (blue) and lipegfilgrastim (green). Results are expressed as % of cycles. Of mote, the overall incidence of all three forms of severe leukocytopenia were low for both the first and all chemotherapy cycles. Differences between both long-acting G-CSFs did not reach statistical significance

Table 2: G-CSF-specific adverse reactions > G1

	Cohort P n (%)	Cohort L n (%)	
Fever (non-FN)	2 (7.4)	1 (3.7)	N.S.
Chills	2 (7.4)	0 (0.0)	N.S.
Fatigue	1 (3.7)	0 (0.0)	N.S.
Bone pain	2 (7.4)	4 (14.8)	N.S.
Leukocytosis > 30 x 10^9/L	1 (3.7)	4 (14.8)	N.S.
Hyperleukocytosis > 60 x 10^9/L	0 (0.0)	1 (3.7)	N.S.

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