Abstract # 1621

PRIMARY PROPHYLAXIS OF FEBRILE NEUTROPENIA USING LONG-ACTING GRANULOCYTE COLONY-STIMULATING FACTORS IN FEMALE PATIENTS RECEIVING DOSE-DENSE BIWEEKLY CHEMOTHERAPY: A SINGLE-INSTITUTION EXPERIENCE

CHRISTIAN M. KURBACHER[1,3], A. TABEA KURBACHER[1], KATJA MONREAL[1], SUSANNE HERZ[1], SANDRA SPERLING[1], JUTTA A. KURBACHER[2]

[1]Division of Gynecologic Oncology and [2]Division of General Gynecology and Obstetrics, Gynecologic Center Bonn-Friedensplatz, Bonn, Germany; [3]Faculty of Medicine, University of Cologne, Cologne, Germany

INTRODUCTION

Recently, dose-dense biweekly chemotherapy (Ctx) regimens gain increasing importance in the treatment of breast cancer and other gynecologic neoplasms. Moreover, many other Ctx regimens used in gynecologic oncology now prescribe a day 1+8 administration followed by only one week Ctx-free break which also fulfills the criterion of dose-dense Ctx (ddCtx). In contrast to conventional q3w or q4w protocols, ddCtx is thought to be associated with a higher risk of severe neutropenia and, consecutively, febrile neutropenia (FN) which – in accordance to international guidelines- 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 is still limited. This single institution non-interventional study was thus 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

53 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 by either PegFG or LipFG. Differences between PegFG and LipFG in regard to WBC, ANC, and ALC were analyzed at BL and for C1-4 separately, by using *student´s* t-tests. Differences between both cohorts regarding the incidence of both hematological complications and G-CSF-related side effects were analyzed by using the Fisher´s exact test. For all statistical calculations a p-value <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: C1, 5.88 vs 12.67, 4.06 vs 12.57, 1.06 vs 1.70; C2, 6.49 vs 12.34, 3.60 vs 10.03, 1.03 vs 1.37; C3, 4.88 vs 17.10, 3.41 vs 12.37, 0.92 vs 1.55; C4, 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 8.0% in cohort P and 0%, 0%, and 4.0% 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%, 3.5%, and 7.0% 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 10^9/L and hyperleukocytosis > 60 x 10^9/L. None of these differences reached statistical significance.

Table 1: Patients´ characteristics

		Cohort P n (%)	Cohort L n (%)	p-value
Total		27 (100)	26 (100)	-
Age (years)	Median Range	53.0 30-78	54.0 39-73	N.S.
Tumor type	Breast Ovarian Others	12 (44.4) 12 (44.4) 3 (11.1)	19 (73.1) 7 (26.9) 1 (3.9)	N.S.
Disease status	Primary Recurrent/metastatic	10 (37.0) 17 (63.0)	13 (50.0) 13 (50.0)	N.S.
Previous chemotherapy	No Yes	10 (37.0) 17 (63.0)	13 (50.0) 13 (50.0)	N.S.

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

	Cohort P n (%)	Cohort L n (%)	p-value
Fever (non-FN)	2 (7.4)	1 (3.8)	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 (15.4)	N.S.
Leukocytosis > 30 x 10^9/L	1 (3.7)	4 (15.4)	N.S.
Hyperleukocytosis > 60 x 10^9/L	0 (0.0)	1 (3.8)	N.S.

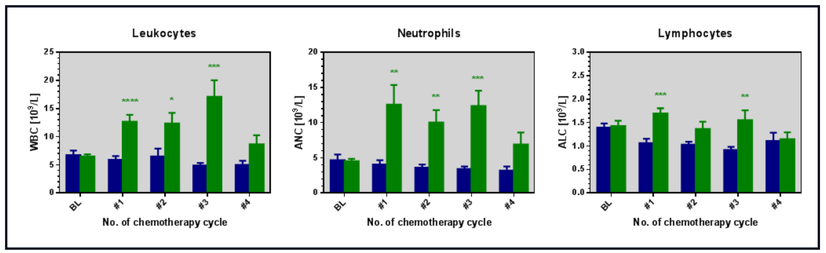

Figure 1: Hematological effectiveness of pegfilgrastim (blue columns) and lipegfilgrastim (green columns). Left, leukocytes; center, neutrophils; right, lymphocytes. Columns show the mean values, error bars represent the SEM. Baseline levels did not differ between cohorts P and L. However, the hematological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

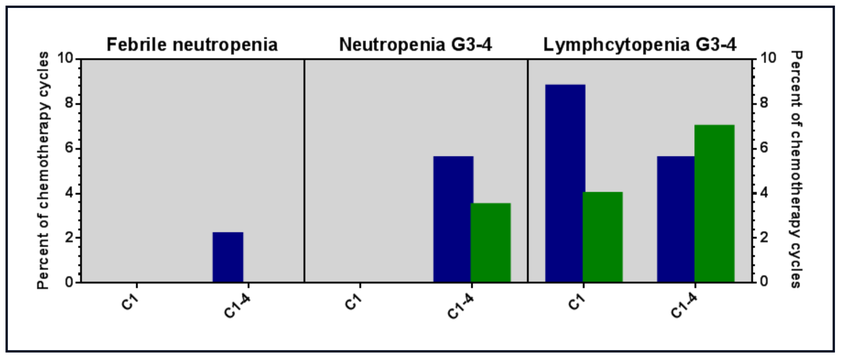

Figure 2: Incidence of febrile neutropenia (left), severe neutropenia (center), and severe lymphocytopenia (right) in dose dense chemotherapy cycles supported by primary prophylaxis with pegfilgrastim (blue) and lipegfilgrastim (green). Results are expressed as percent of cycles. Of note, the overall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

CONCLUSIONS

- Caveats:

(1) Two-cohort non-interventional study, not a controlled randomized trial.

(2) Both cohorts 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 are 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.

Contact: Christian M. Kurbacher, M.D.; Ph.D.,
Medical Director
Gynecologic Center Bonn-Friedensplatz; Friedensplatz 16; 53111 Bonn, Germany
Phone: +49 228 22720340; Fax: +49 228 22720114
e-mail: Praxis.Kurbacher@online.ms