An Open-Label Multicenter Safety, Tolerability, and Efficacy Study of Recombinant Granulocyte Colony-Stimulating Factor in the Prevention of Neutropenic Complications in Breast Cancer Patients

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Key words: *rG-CSF; open-label multicenter study; breast cancer; safety; neutropenic complications.*

Summary. *The primary objective of this open-label, two chemotherapy arm, phase 4 study was to evaluate the safety and efficacy of newly developed recombinant granulocyte colony-stimulating factor (rG-CSF) used to prevent neutropenia-related complications in patients with metastatic breast cancer treated with docetaxel (75 mg/m^2) and doxorubicin (50 mg/m^2) or docetaxel (100 mg/m^2) alone.*

Material and Methods. A total of 50 patients who were treated with a maximum of 6 cycles of either docetaxel-doxorubicin (36 patients) or docetaxel alone (14 patients) every 21 days were recruited from 3 centers in Lithuania. All the patients received study medication rG-CSF at a dosage of 5 μg/kg per day (Sicor Biotech UAB, Teva Group) from day 2 of each cycle and continued for minimum 5 days or until absolute neutrophil count reached $\geqslant 1.5\times10^9$/L.

Results. A total of 611 adverse events were reported. Most of them were related to myelotoxic chemotherapy. Two patients withdrew due to adverse events (neuropathy and bone pain). One patient died possibly because of pulmonary thromboembolism. The most frequently reported adverse events related to study drug in the docetaxel-doxorubicin and docetaxel groups were leukocytosis (22% and 21%, respectively), bone pain (19% and 21%, respectively), and headache (8% and 14%, respectively). The incidence of grade 4 neutropenia in both the groups was 47% and 29%, respectively, in all cycles and 42% and 21%, respectively, in cycle 1. The incidence of febrile neutropenia was 8% in cycle 1 and 14% across all cycles. The mean duration of febrile neutropenia was 2.1 days (SD, 1.9) in cycle 1 and 2.14 days (SD 2.0) across all cycles in both the treatment groups.

Conclusion. This study provide data that the study drug rG-CSF has the expected safety and could be an efficacious medication to decrease the risk of febrile neutropenia and related complications of myelosuppressive chemotherapy in patients with metastatic breast cancer.

Introduction

Chemotherapy-induced neutropenia and infection has negative consequences including hospitalization, administration of antibiotics, reduced quality of life, delays/reductions of chemotherapy dose, reduced treatment effectiveness, and increased healthcare expenditures (1). Safe, effective, and rational prevention of neutropenia is a goal of daily practice in oncology for both patient safety and cost efficiency. Granulocyte colony-stimulating factor (G-CSF) is a recombinant protein containing 175 amino acid residues that is produced by recombinant DNA technology through the expression of the human G-CSF encoding gene inserted into *E. coli* bacteria. The recombinant G-CSF (rG-CSF) was developed by the Sicor Biotech UAB (Teva Group), Lithuania, and approved for use in patients receiving myelosuppressive anticancer chemotherapy to prevent neutropenia-related complications, such as cases of febrile neutropenia (FN), in patients with severe chronic neutropenia, cancer patients receiving bone marrow transplant, and patients undergoing peripheral blood progenitor cell collection (2, 3).

The primary objective of this open-label, nonrandomized study was to evaluate the safety and tolerability of new rG-CSF by assessing the incidence of adverse events (AEs), abnormalities in laboratory parameters, and anti-G-CSF antibody formation.

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The secondary objectives were the efficacy of new rG-CSF used to prevent neutropenia-related complications in patients with metastatic breast cancer.

Materials and Methods

Patients and Study Design. This 13-month, open label, two chemotherapy arms, phase 4 study was carried out in three centers in Lithuania between March 2004 and November 2005. The protocol was approved by the State Medicines Control Agency and Ethics Committee. Written informed consent was obtained from all patients before any study-related procedure was performed. The study was conducted in accordance with good clinical practice and met the standards of the Declaration of Helsinki. Eligible female patients were administered one of the two following chemotherapy regimens: either doxorubicin (intravenous bolus injection) at a dosage of 50 mg/m^2 per day on day 1 every 3 weeks and docetaxel (intravenous infusion) at a dosage of 75 mg/m^2 per day 1 hour after doxorubicin injection, or docetaxel (intravenous infusion) at a dosage of 100 mg/m^2 per day on day 1 every 3 weeks. The patients received 1 to 6 chemotherapy cycles as decided according to the usual clinical practice. Women were eligible for the study entry if they met the following inclusion criteria: $\geqslant$18 years of age, diagnosis of metastatic breast cancer, previous chemotherapy completed more than 4 weeks before inclusion into the study, performance status $\leqslant$2 according to the Eastern Cooperative Oncology Group (ECOG) scale, probable life expectancy of at least 6 months, absolute neutrophil count (ANC) of $\geqslant 1.5\times10^9$/L, adequate hepatic and cardiac functions. The patients were excluded from the study if they had radiation therapy within 2 weeks before the screening visit, bone marrow or stem cell transplantation, a cumulative dose of doxorubicin >240 mg/m^2 or epirubicin >600 mg/m^2 in case of doxorubicin + docetaxel combination therapy, and left ventricle ejection fraction <50% (by echocardioscopy) for patients selected for docetaxel and doxorubicin treatment.

Study Drug. All eligible patients received medicinal product rG-CSF at a dosage of 5 μg/kg per day based on their actual body weight (Sicor Biotech UAB, Teva Group). Daily subcutaneous injections of study medicinal product were administered starting day 2 of each chemotherapy cycle, 24 hours after chemotherapy completion, that continued either for minimum 5 days or until documented ANC of $\geqslant 1.5\times10^9$/L after nadir.

Study Assessments. The safety endpoint of this study was assessed by the incidence of AEs, severity and incidence of AEs requiring concomitant treatment, discontinuations, abnormal changes in laboratory parameters, and antibody formation to new rG-CSF. Serum samples for antibody testing were collected during study product treatment and analyzed for anti-G-CSF antibodies by qualitative and quantitative methods including ELISA, xMAP, neutralizing assay, Western blot, and Biacore. The efficacy endpoints were incidence and duration of FN, duration of fever, incidence of subsequent chemotherapy cycle delays, decrease in chemotherapy doses, and incidence of used antibiotic therapy.

Statistical Analysis. Descriptive statistics for each variable include the arithmetic mean (arithm. mean), standard deviation (SD), and range. The data analysis was carried out on the "intent-to-treat" (ITT) basis to include all the patients who received at least one injection of rG-CSF.

Results

Demographic Characteristics of Patients and Distribution. Fifty patients were recruited at three centers in Lithuania from March 2004 and November 2005. All patients were female Caucasian, with a mean age of 53.54 years (SD, 10.47), mean body weight of 73.66 kg (SD, 18.69), and mean height of 163.03 cm (SD, 6.42). The mean body weight of the patients was 78.18 kg (SD, 26.59) in the docetaxel group and 71.90 kg (SD, 14.65) in the docetaxel-doxorubicin group (P>0.05). Demographic characteristics of the patients are presented in Table 1. In total, 273 cycles of chemotherapy were administered to 50 patients. Thirty-six patients (195 cycles) received docetaxel and doxorubicin at a dosage of 75 mg/m^2 and 50 mg/m^2, respectively, and 14 patients (78 cycles) received docetaxel at a dosage of 100 mg/m^2. There was no prespecified agreement regarding a specific proportion of patients that should be allocated to either of these two chemotherapy groups. All study patients received at least

Table 1. Demographic and Clinical Characteristics of the Patients by Treatment Group

Characteristic	Doxorubicin-Docetaxel Group (ITT, n=36)	Docetaxel Group (ITT, n=14)
Age, mean (SD) [range], years	52.14 (10.22) [33–72]	57.24 (10.62) [34–74]
Weight, mean (SD), kg	71.90 (14.65)	78.18 (26.59)
Body mass index, mean (SD), kg/m^2	26.85 (5.23)	30.03 (9.63)
Chemotherapy naïve, n (%)	21 (58)	1 (7)
Radiotherapy naïve, n (%)	23 (64)	4 (29)
Baseline ANC, mean (SD) [range], $\times10^9$/L	4.62 (2.10) [1.84–11.48]	4.76 (2.12) [2.16–8.91]

ANC, absolute neurophil count.

one cycle of study medicinal product at a dosage of 5 μg/kg per day. The mean duration of treatment with rG-CSF injections administered to patients in cycle 1 was 6.9 days (SD, 1.73), and the mean cumulative exposure was 368 μg/kg (SD, 90.0). The mean number of rG-CSF injections used per cycles 2 to 6 was 6.3 days (SD, 1.4). The mean cumulative exposure during cycles 2 to 6 was 365 μg/kg (SD, 91.8). In total, 8 patients discontinued study participation. Two patients withdrew from the docetaxel group and 6 patients from the docetaxel-doxorubicin group. Three patients withdrew due to AEs (2 from the docetaxel group and 1 from the docetaxel-doxorubicin group). There were other 5 withdrawals: 3 due to disease progression, and 2 for noncompliance with inclusion/exclusion criteria.

Safety

Adverse Events. Most AEs were associated with the administration of myelosuppressive chemotherapy (Table 2). The overall incidence rates of AEs were 8% and 13% in both the groups, respectively. In general, rG-CSF was well tolerated. A total of 57 AEs in 24 patients were reported as related to the study drug. In the docetaxel-doxorubicin treatment group (33 study drug-related AEs), the following AEs were reported most frequently: leukocytosis (22%), bone pain (19%), headache and arthralgia (8% each). In the docetaxel treatment group (24 study drug-related AEs), the following AEs were reported most frequently: bone pain and leukocytosis (21% each), headache and musculoskeletal pain (14% each), and back pain (7%). Most events were mild to moderate in severity and did not require treatment except for cases of bone pain when non-narcotic analgetics (500-mg paracetamol) were prescribed. There were 16 serious AEs in 13 patients (incidence, 2%). All of them were related to myelosuppressive chemotherapy. Twelve serious AEs occurred in the docetaxel/doxorubicin group and 4 in the docetaxel group. Three patients withdrew from the study due to AEs: one patient due to a docetaxel-related AE (neuropathy), a second due to a study-drug related AE (musculoskeletal pain), and a third patient died. Although the autopsy was refused by the relatives of the patient, the possible cause of this sudden death was pulmonary thromboembolism. This sudden death was considered as not related to the study medicinal product.

Laboratory Values. The most frequently reported grade 3/4 laboratory abnormality, using the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI), was neutropenia. This parameter was of special interest in this study. The incidence of neutropenia (grade 3/4) in all cycles of the study was 80% and 50% in the docetaxel-doxorubicin and docetaxel groups, respectively. In cycle 1, this incidence was 61% and 43%, respectively. The incidence of grade 4 neutropenia in all cycles and cycle 1 was 47% and 29% vs. 42% and 21% in the docetaxel-doxorubicin and docetaxel groups, respectively. Mild-to-moderate decreases in other hematological parameters including leukocyte, lymphocyte, and platelet counts were reported occasionally. Isolated cases of reversible and slight elevations in alkaline phosphatase and lactate dehydrogenase levels and reductions in calcium and sodium concentrations occurred in both treatment groups.

Table 2. Incidence of the Most Frequently Reported Adverse Events by Treatment Groups

Adverse Event	Incidence in Cycle 1 (%)/ All Cycles (%) in the Doxorubicin-Docetaxel Group (n=36)	Incidence in Cycle 1 (%)/ All Cycles (%) in the Docetaxel Group (n=14)
Alopecia	61/16	50/14
Nausea	53/28	21/9
Pyrexia	33/10	50/19
Bone pain	33/8	21/6
Dyspepsia	33/14	7/3
Asthenia	31/11	43/22
Dyspnea	6/3	36/14
Leukocytosis	22/5	21/5
Headache	22/4	14/5
Anorexia	19/5	14/3
Stomatitis	19/8	14/6
Fatigue	14/5	14/3
Arthralgia	14/4	7/3
Constipation	11/4	14/3
Anemia	11/3	7/3
Insomnia	11/3	21/4
Pain in extremity	11/3	14/3
Vomiting	11/3	14/3
Dyspnea	6/3	33/14
Musculoskeletal pain	3/1	14/3
Diarrhea	8/2	21/5
Neutropenia (all grades)	8/2	14/3

Antibody Formation. Serum samples for antibody testing were collected, and no positive binding or neutralizing antibodies were detected in any patient.

Efficacy

Incidence and Duration of Febrile Neutropenia. FN was defined as a temperature >38.5°C and ANC $<0.5\times10^9$/L according to the guidelines developed by the European Society of Medical Oncology (ESMO). The incidence rate of febrile neutropenia was defined as the number of patients that developed FN in at least one chemotherapy cycle. In the docetaxel-doxorubicin treatment group, 3 patients (8%) experienced FN in cycle 1. In cycles 2 to 6, 4 patients (11%) in the docetaxel-doxorubicin group had FN episodes. No significant difference in the incidence of FN was observed comparing cycle 1 and cycles 2 to 6 (P=0.7055). The highest number of episodes of FN (n=3) developed during cycle 1 of docetaxel/doxorubicin chemotherapy, as it

Table 3. Incidence and Duration of Febrile Neutropenia by Treatment and Cycle

	Docetaxel-doxorubicin Treatment Group (n=36)		Docetaxel Treatment Group (n=14)	
	No. of Patients	Incidence, %	No. of Patients	Incidence, %
Incidence of FN				
Cycle 1	3	8	–	–
Across all cycles	5	14	–	–
	No. of FN	Duration, days	No. of FN	Duration, days
Duration of FN				
Cycle 1	3	2.0	–	–
Across all cycles	7	2.14	–	–

FN, febrile neutropenia.

might be expected, because the myelotoxic effects of chemotherapy are most prominent in cycle 1. Total incidence rate of FN was 14%. No FN occurred in the docetaxel treatment group (Table 3). The duration of FN was defined as the number of consecutive days when ANC was $<0.5\times10^9$L and temperature was >38.5°C. In cycle 1, the mean duration of FN was 2.0 days (SD, 1.9) and in cycles 2 to 6, it was 2.3 days (SD, 2.0).

Duration of Fever. The onset of fever was considered the elevation of axillary temperature ⩾38.0°C. In cycle 1, the mean duration of fever was 3.3 days (SD, 3.4) and 3.0 days (SD, 2.7) in the docetaxel-doxorubicin and docetaxel groups, respectively. In cycles 2 to 6, the mean duration of fever was 3.6 days (SD, 3.5) in the docetaxel-doxorubicin and 2.1 days (SD, 1.4) in the docetaxel group. There was no significant difference in the duration of FN comparing cycle 1 and cycles 2 to 6 (P=0.6965).

Incidence of Chemotherapy Delays and Chemotherapy Dose Reduction. The incidence rate of chemotherapy dose reduction was defined as the ratio of cycles with reduced chemotherapy dose to cycles with the same chemotherapy dose as in the previous cycle. Of the 36 patients administered docetaxel-doxorubicin therapy, 3 experienced chemotherapy delays (2%). Of the 14 patients in the docetaxel treatment group, 1 patient experienced chemotherapy delay. Across all cycles, of the 50 patients, there were 4 cases of delays of subsequent chemotherapy cycles with an approximately 1% incidence rate per cycle.

Incidence of Antibiotic Therapy. The incidence of antibiotic therapy used was defined as the percentage of patients with the systemic use of antibiotics (intravenous, intramuscular, or oral routes) in at least one cycle. The incidence rate of antibiotics used intravenously was 20% among patients or 7% among cycles (10 patients were treated by intravenous antibiotics) in both the treatment groups. Seven patients (19%) in the docetaxel/doxorubicin group and 3 patients (21%) in the docetaxel group received intravenous antibiotics.

Discussion

This open-label, multicenter, phase 4 study presents data that in patients with metastatic breast cancer, subcutaneous injections of rG-CSF at a dosage of 5 μg/kg per day were well tolerated and efficacious in the prevention of chemotherapy-induced febrile neutropenia and neutropenic complications. Evaluations of both safety and efficacy parameters of study medicinal product rG-CSF collected in this study were compared with the published data on the use of reference medicinal product containing recombinant G-CSF (Neupogen™). Most of the adverse events in this study were very similar to the events in the groups of myelosuppressive chemotherapy with CSFs support (4). Leukocytosis, bone pain, and headache were the most frequently reported AEs related to the study drug. During this study, leukocyte counts were raised to a maximum level of 48 000/mm^3 (5). According to numerous publications, marked leukocytosis (occasionally ⩾100 000/mm^3) may occur in cancer patients receiving G-CSF and chemotherapy, and it is predictable and related to the pharmacodynamic action of the drug (4, 6). It is considered that such an increase in leukocyte count is not associated with any clinically significant harmful effects, although it is recommended to monitor leukocyte count to avoid any potential complications (7, 8). Bone pain is referred to as the most frequent adverse event in all patients receiving recombinant G-CSF. In this study, the incidence of bone pain was about 24% and did not exceed the incidence specified in the prescribing information of reference medicinal product. Data on headache and other adverse events associated with rG-CSF vary across various publications, but the incidences of these events were similar to that described in the prescribing information of Neupogen™ (9). The possible cause of one case of sudden death reported during the study was suspected pulmonary thromboembolism. It is well known that patients with cancer have an increased risk of developing venous thromboembolism due to a hypercoagulable state associated with malignancy. Epidemiological data indicate that thrombosis is the second leading cause of mortality in cancer patients, second only to cancer itself (10). The highest prevalence of venous thromboembolism is found in patients with breast, colorectal, and lung cancer (11). The published data demonstrate a higher incidence of severe and clinically significant neutropenia (grade 4) and supportive evidence that the administration of study medicinal product rG-CSF decreases the frequency of severe neutropenia (12).

The main efficacy endpoint of this study – the incidence of FN – was found to be comparable with

that reported in other studies. A study by Holmes et al., examining 24 breast cancer patients treated with similar treatment regimens including rG-CSF, reported that 12% of the patients developed FN in all cycles (13). Similar results as we obtained in our study were presented in another study conducted by Holmes et al. The incidence of FN in breast cancer patients receiving Neupogen™ was 12% in cycle 1 and 18% across all cycles (14). Most treatment regimens administered to patients with breast cancer are adjuvant therapies associated with an intermediate-to-high risk of FN in the absence of growth factor support. Brain et al. reported a 40.8% incidence of FN in patients with breast cancer who were administered the doxorubicin-docetaxel regimen similar to our study (doxorubicin, 50 mg/m^2, plus docetaxel, 75 mg/m^2) (15). Soong et al. assessed the data gathered from breast cancer patients receiving docetaxel and cyclophosphamide and noted a 50% incidence of FN (16). The patients in both the studies did not receive any growth factor.

Limitations of the study are small sample size and open, nonrandomized design. Moreover, our analysis did not include any control group or chemotherapy patients who did not receive any rG-CSF; therefore, comparisons based on literature data are limited. In the present study, rG-CSF was administered 24 hours after chemotherapy as indicated in the product labeling. According to routine clinical practice, treatment with growth factors can be initiated on day 5 or 6 of each cycle (17). These controversies should be investigated more precisely in the future.

Nonetheless, the results of this study, which involved an apparently representative cohort of patients with metastatic breast cancer, provide useful and clinically relevant information on the use of new rG-CSF formulation.

Conclusion

The results demonstrated that the study drug rG-CSF was well tolerated and could be used as an efficacious drug to decrease the risk of febrile neutropenia and related complications of myelosuppressive chemotherapy in patients with metastatic breast cancer treated with heterogeneous chemotherapy regimens.

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Statement of Conflict of Interest

Audrius Sveikata contributed to the study design, the assessment and interpretation of data. Other authors – Sigita Liutkauskienė, Elona Juozaitytė, Laimutė Tamošaitytė, and Dainius Characiejus – were the principal investigators and investigators of the study financed by the Sicor Biotech (Teva Group). Kastytis Šeštakauskas was an employee of the Sicor Biotech (Teva Group) at the time of study. No other conflicts of interest are stated.

Atvirasis daugiacentris granuliocitų kolonijas stimuliuojamojo faktoriaus, skiriamo sergančiosioms krūties vėžiu neutropenijos sukeltų komplikacijų profilaktikai, saugumo, toleravimo ir veiksmingumo tyrimas

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Raktažodžiai: rGKSF, atvirasis daugiacentris tyrimas, krūties vėžys, saugumas, neutropenijos komplikacijos.

Santrauka. *Tyrimo tikslas.* Pirminis šio atvirojo dviejų gydymo grupių IV fazės tyrimo tikslas buvo rekombinacinio granoliocitų kolonijas stimuliuojamojo faktoriaus (rGKSF), vartojamo neutropenijos sukeltų komplikacijų profilaktikai, saugumas ir veiksmingumas sergančiosioms metastazavusiu krūties vėžiu ir gydomoms 75 mg/m^2 docetakseliu ir 50 mg/m^2 doksorubicinu arba tik 100 mg/m^{2}docetakseliu.

Tiriamųjų kontingentas ir tyrimo metodai. Lietuvoje trijuose centruose buvo atrinkta 50 ligonių, kurios kasdien, 21 dieną, daugiausia šešis ciklus buvo gydomos docetakseliu ir doksorubicinu (n=36) arba vien docetakseliu (n=14). Visoms ligonėms kasdien buvo skiriama po 5 mikrogramus kilogramui kūno svorio per parą tiriamojo preparato – rGKSF (Sicor Biotech UAB, Teva Group). rGKSF buvo injekuojama po oda

pradedant nuo antrosios kiekvieno ciklo dienos, mažiausiai skiriama penkias dienas arba iki tol, kol absoliutus neutrofilų skaičius (ANS) bus $\geqslant 1{,}5\times10^9$/L.

Rezultatai. Iš viso pasireiškė 611 nepageidaujamų reiškinių. Dauguma jų buvo susiję su kaulų čiulpams toksiniu gydymu (chemoterapija). Dvi ligonės iš tyrimo buvo pašalintos dėl nepageidaujamų reiškinių (neuropatija ir kaulų skausmas). Viena ligonė mirė. Mirtį sukėlė plaučių trombembolija. Dažniausiai pasireiškę nepageidaujami reiškiniai, susiję su tiriamuoju preparatu, buvo leukocitozė (22 proc. – docetakselio ir dosorubicino, 21 proc. – vien docetakselio grupėje); kaulų skausmas (19 proc. – docetakselio ir dosorubicino, 21 proc. – vien docetakselio grupėje); galvos skausmas (8 ir 14 proc., atitinkamai). IV laipsnio neutropenijos dažnis visuose cikluose buvo 47 ir 29 proc.; pirmojo ciklo metu atitinkamai – 42 ir 21 proc. gydymo grupėse. Febriliosios neutropenijos dažnis pirmojo ciklo metu buvo 8 proc., per visus ciklus – 14 proc. Vidutinė febriliosios neutropenijos trukmė pirmojo ciklo metu buvo 2,1 dienos (standartinis nuokrypis – 1,9), o per visus ciklus – 2,14 dienos (standartinis nuokrypis – 2,0) abiejose gydymo grupėse.

Išvados. Šio tyrimo rezultatai rodo, kad rGKSF yra saugus ir gerai toleruojamas ir gali būti veiksmingas mažinant febriliosios neutropenijos ir su ja susijusių komplikacijų riziką metastazavusiu krūties vėžiu sergančioms ligonėms, vartojančioms toksinę kaulų čiulpams chemoterapiją.

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