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Clinical Study

A Phase IV Clinical Trial of Patients with Solid Tumors Receiving Lenograstim as Primary Prophylaxis for Chemotherapy-Induced Neutropenia, in a Docetaxel-Based Regimen

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Docetaxel-based chemotherapy regimens have substantially improved survival and recurrence rates for cancer patients. Safety profile of docetaxel regimens includes toxicities, particularly a high risk of neutropenia and febrile neutropenia. Granotax was a prospective, open label, multicentre, national phase IV study that evaluated the incidence and severity of neutropenia in adult patients with solid tumors being treated with a docetaxel-based regimen while receiving the GCSF lenograstim. Among the 394 enrolled patients the incidence of grade 3-4 neutropenia was 16.2% and of febrile neutropenia was 1.5%, far lower than the reported 85–100% and 30–40% incidence without G-CSFs. A total of 68 patients (17.3%) were reported to have experienced at least one grade 3-4 adverse event during the study. Two (0.5%) patients and 32 (8.1%) patients had dose delayed due to febrile neutropenia and neutropenia, respectively. Four (1.0%) patients and 32 (8.1%) patients had a dose changed due to febrile neutropenia and neutropenia, respectively. The low incidence of adverse effects and chemotherapy dose changes, delays, and withdrawals supports the use of lenograstim as effective primary prophylaxis in South African patients being treated with a docetaxel-based regimen. Furthermore, lenograstim may increase the patient's exposure to chemotherapy allowing patients to receive optimal dosing and duration of treatment, benefitting survival.

1. Introduction

South Africa is ranked 50th on the World Cancer Research Fund's list of countries with the highest cancer prevalence [1] and has recently been predicted to have a 78% increase in cancer cases by 2030 [2]. Breast cancer is the number one cancer diagnosed amongst South African women with a 1 in 29 lifetime risk [2, 3], while prostate cancer is the most prevalent in men [4]. Nevertheless, treatment options have substantially improved survival rates. Systemic adjuvant chemotherapy with anthracycline- and taxane-containing regimens has become the standard first line treatment for early and metastatic breast cancer [5], with large phase III randomized trials showing extremely high long-term disease-free survival and overall survival rates (resp., 80% and 90% at 5 years and 70% and 80% at 8 years) [6]. Indeed, a recent meta-analysis of data from 44,000 early breast cancer patients showed that the addition of a taxane such as docetaxel in anthracycline regimens reduces mortality by an average of ~33%. Furthermore, this is largely independent of age, nodal status, tumor diameter or differentiation, estrogen receptor status, or tamoxifen use [7].

These improvements in outcome are very welcome, yet they do have associated substantial toxicities, especially a moderate-to-high risk of neutropenia or febrile neutropenia (FN) [8]. Such adverse effects are serious and can be life-threatening and commonly occur during the initial cycles of cytotoxic therapy [8–10]. Furthermore, they can lead to delays

and dose reductions in chemotherapy treatment, thereby potentially compromising the efficacy of chemotherapy and, consequently, patient outcome [10]. In fact, reducing the planned dose intensity of systemic adjuvant chemotherapy regimens by as little as 15% has been shown to significantly reduce time to progression and overall survival rates in women with metastatic breast cancer [5].

There is strong and consistent clinical evidence to show that granulocyte-colony stimulating factors (G-CSFs) reduce the risk of chemotherapy-induced neutropenia and therefore complicated neutropenia and can be used to maintain chemotherapy at the desired dose intensity or density and minimize delays in treatment [11]. G-CSFs have been shown to reduce overall mortality risk [8, 11], reduce the incidence of other adverse events (grade 2 or greater anaemia, asthenia, anorexia, myalgia, nail disorders, and oral mucositis) associated with docetaxel-based chemotherapy regimens, and increase health related quality of life and consequently treatment compliance [8, 12]. Based on this evidence, guidelines published by the American Society of Clinical Oncology and the European Organisation for Research and Treatment of Cancer state that when the overall risk of FN is 20% or greater, especially on "dose dense" regimens, primary prophylaxis with G-CSFs is justified [10, 13].

The current study is the first to focus on South African patients in a real life setting. The primary objective was to evaluate the incidence and severity of neutropenia in those being treated for solid tumors with a docetaxel-based regimen when the G-CSF, lenograstim, is used as a primary prophylaxis for chemotherapy-induced neutropenia. Secondary objectives included evaluating similarly the incidence and severity of FN (with or without antibiotics). Further nonhematological secondary objectives included evaluating the incidence and severity of asthenia, anorexia, myalgia, nail changes, and oral mucositis adverse events and recording neutropenia/FN associated days in hospital, infections, use of anti-infectives, and chemotherapy dose changes, withdrawals, or treatment delays.

2. Methods

Granotax (NCT01107756) was a prospective, open label, national multicentre, phase IV postmarketing study that evaluated the incidence and severity of neutropenia in adult patients with solid tumors being treated with a docetaxel-based regimen while receiving the G-CSF lenograstim.

2.1. Patients. The study protocol was approved by the independent institutional review boards of each site and a written informed consent was obtained from patients before study entry, in accordance with the Declaration of Helsinki [14]. Adult patients (≥21 years) were enrolled in the survey from 27 medical centers across South Africa. Patients with a histological diagnosis of breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, prostate cancer, or head and neck cancer to be treated with a docetaxel-based chemotherapy regimen and who had not previously been treated on a docetaxel-based chemotherapy regimen were eligible for inclusion in the study. Patients with severe impairment in biochemistry or bone marrow function, known hypersensitivity to lenograstim, its constituents, docetaxel or polysorbate 80, or taking contraindicated drugs were excluded from the study. Patients who were concurrently being treated with radiotherapy were also excluded. The planned sample size was 400–500 patients.

2.2. Treatment. All patients enrolled in the study were treated on a docetaxel-based chemotherapy regimen (either docetaxel alone or in combination). Lenograstim was to be administered with every cycle of chemotherapy. Treatments were given in accordance with the physicians' current practice, clinical guidelines, and ethical considerations, with guidance from the prescribing information in South Africa, according to Medicines Control Council (MCC) registration. Patients were monitored according to the study protocol until the scheduled date of study completion or up to recovery or stabilization of a followed-up AE, whichever came last. The patient or physician could decide to withdraw from the treatment at any time for any reason.

2.3. Efficacy Assessments. Since the primary criteria were safety parameters, these events were recorded as outcomes as well as adverse events. All adverse events were graded according to the CTCAE version 4.03 classification system. Specifically, the incidence and severity of neutropenia, FN, anaemia, asthenia, myalgia, oral mucositis, and nail changes were recorded from the first treatment dose up until 30 to 90 days following the last treatment visit. Haematological tests were performed according to the treating physician's usual practice and values were collected and recorded in the case report form (CRF).

2.4. Safety Assessments. Safety measurements collected throughout the study included all other adverse events (excluding the primary and secondary criteria of the study), clinical laboratory assessments (hematology and clinical chemistry), and physical examination findings. All these measurements were performed and collected according to the standard of practice at the investigator site. Records were made of the number of neutropenia/FN associated stays in hospital, infections, use of anti-infectives, and chemotherapy dose changes, withdrawals, and treatment delays.

2.5. Statistical Analysis. Data from all the participating centers in South Africa were combined and treated as one dataset for the purposes of the analysis. The statistical analysis of the survey was of a descriptive nature where continuous variables were summarized by mean, median, standard deviation, and minimum and maximum values and discrete variables were summarized by frequencies and percentages.

All analyses were carried out on SAS, Release 9.2, run under Microsoft Windows for a personal computer.

Table 1: Patient and cancer baseline characteristics.

Baseline characteristic	Number of patients (%)
Sex	
Male	49 (12)
Female	345 (88)
Age (years)	
Median	54
Range	26–88
ECOG performance status	
Grade 0	232 (58.9)
Grade 1	128 (32.5)
Grade 2	11 (2.8)
Grade 3	1 (0.3)
Grade 4	0
Unknown	22 (5.6)
Breast cancer	318 (80.7)
Non-small cell lung cancer	14 (3.6)
Ovarian cancer	14 (3.6)
Hormone refractory prostate cancer	18 (4.6)
Nonhormone refractory prostate cancer	6 (1.5)
Gastric cancer	14 (3.5)
Head and neck cancer	10 (2.4)

The percentage is calculated out of the 394, the total number of patients in the study's cohort for sex, age, ECOG status, and cancer type.

3. Results

3.1. Patients. Patients were recruited from 26 March 2010, with the last patient completing on 11 May 2012. A total of 394 patients (345 female) enrolled in the study, of whom the vast majority were being treated for breast cancer (81% of the total cohort). The median age of the study population was 54 years (min–max: 28–88 years). A total of 360 (92%) patients had an ECOG performance status ≤1 (Table 1).

3.2. Efficacy Outcomes. In the Granotax study patients were treated with a docetaxel-based chemotherapy regimen for solid tumors. 16.5% of patients were treated with a single agent docetaxel-based chemotherapy. 30.5% of patients received concurrent combination chemotherapy and 53.0% patients received combination sequential treatment. 74.8% of patients were treated in the adjuvant/neoadjuvant setting, 16.2% in the first line metastatic setting, and 8.9% in ≥2nd line metastatic setting.

The following combination concurrent regimens were most commonly used: docetaxel + cyclophosphamide (TC), docetaxel plus carboplatin (TCb), and docetaxel, cisplatin + 5FU (DCF).

The median dosage of docetaxel given in these regimens was 75 mg/m^2 on a 3-weekly schedule.

The following combination sequential regimens were commonly used: doxorubicin, cyclophosphamide followed by docetaxel (AC-T);5 FU, epirubicin, cyclophosphamide followed by docetaxel (FEC-T); doxorubicin, cyclophosphamide followed by docetaxel and trastuzumab (AC-T + H).

Table 2: Incidence of neutropenia, febrile neutropenia, and other adverse effects.

	All grades, *n* (%)	Grade 3-4, *n* (%)
Neutropenia	137 (34.8)	64 (16.2)
Febrile neutropenia	6 (1.5)	6 (1.5)
Anaemia	214 (54.3)	5 (1.3)
Anorexia	49 (12.4)	2 (0.5)
Asthenia	183 (46.4)	16 (4.1)
Myalgia	182 (46.2)	20 (5.1)
Oral mucositis	147 (37.3)	6 (1.5)
Nail discolouration	91 (23.1)	—
Nail ridging	35 (8.9)	—
Nail loss	14 (3.6)	—

The percentage is calculated out of the 394, the total number of patients in the study's cohort.

The median dose of docetaxel used in the combination sequential regimen was 100 mg/m^2 on a 3-weekly schedule.

Docetaxel as a single agent was given at a mean dosage level of 80 mg/m^2 on a 3-weekly schedule.

The median number of lenograstim vials used per patient per cycle was 5.0. 49 (12.4%) patients had a recorded change in the lenograstim treatment. Changes in lenograstim treatment were recorded as dose reductions and dose delays, as well as an increase in the dose compared with the preceding cycle of treatment. The reasons for these changes were recorded as asthenia (0.25%), myalgia (1.0%), neutropenia (3.3%), infections other than febrile neutropenia (0.25%), febrile neutropenia (0.51%), other adverse events (0.76%), and other (7.4%). Some patients reported multiple reasons for treatment changes.

Grade 3-4 FN and neutropenia in the total patient cohort were reported in 6 (1.5%) and 64 (16.2%) patients, respectively. 120 patients were treated on the docetaxel combination concurrent regimen. 1.7% of these patients (2/120) experienced febrile neutropenia and 21.7% (26/120) experienced grade 3-4 neutropenia. 209 patients were treated on the combination sequential regimen. 1.0% (2/209) of patients experienced febrile neutropenia and 15.3% (32/209) of patients experienced grade 3-4 neutropenia. 65 patients were treated on the docetaxel single agent regimen. 3.1% (2/65) experienced febrile neutropenia and 15.3% (10/65) experienced grade 3-4 neutropenia. Some patients changed between chemotherapy regimens during the course of the study and incidence of febrile neutropenia and grade 3-4 neutropenia for a specific patient could be reflected in more than one treatment regimen.

Neutropenia, febrile neutropenia, and other secondary outcome measures are listed in Table 2.

3.3. Safety Outcomes. The safety data reported here does not include the primary and secondary objectives related adverse events of neutropenia, FN, asthenia, anorexia, myalgia, oral mucositis, or nail changes. 378 (95.9%) patients experienced at least one adverse event (all grades), and 68 (17.3%) patients experienced at least one grade 3-4 adverse event (Table 3).

Table 3: Adverse effects not related to primary and secondary objectives, regardless relationship with chemotherapy.

Adverse effect	All Grades *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 5 *n* (%)
Embolism	1 (0.25)	—	—	1 (0.25)
Intracranial haemorrhage	1 (0.25)	—	—	1 (0.25)
Abdominal pain/discomfort	69 (17.5)	4 (1.0)	—	—
Alopecia	69 (17.5)	1 (0.25)	—	—
Arthralgia	36 (9.1)	2 (0.5)	—	—
Back pain	56 (14.2)	5 (1.2)	—	—
Bone pain	29 (7.3)	4 (1.0)	—	—
Constipation	88 (22.3)	1 (0.25)	—	—
Diarrhoea	138 (35.0)	8 (2.0)	1 (0.25)	—
Disease progression	18 (4.6)	1 (0.25)	2 (0.5)	—
Dizziness	23 (5.8)	2 (0.5)	1 (0.25)	—
Drug hypersensitivity	10 (2.5)	1 (0.25)	1 (0.25)	—
Dyspnoea	40 (10.2)	5 (1.2)	1 (0.25)	—
Fatigue	74 (18.8)	3 (0.8)	—	—
Flushing	37 (9.4)	2 (0.5)	—	—
Headache	71 (18.0)	—	1 (0.25)	—
Insomnia	40 (10.2)	1 (0.25)	—	—
Nausea	130 (33.0)	3 (0.8)	—	—
Peripheral neuropathy	33 (8.4)	2 (0.5)	—	—
Oedema	77 (19.5)	1 (0.25)	—	—
Oropharyngeal pain	31 (7.9)	1 (0.25)	—	—
Pain	57 (14.5)	2 (0.5)	—	—
Palmar-plantar erythrodysaesthesia syndrome	11 (2.8)	2 (0.5)	—	—
Cough	26 (6.6)	1 (0.25)	—	—
Pyrexia	13 (3.3)	—	1	—
Rash	59 (15.0)	2 (0.5)	—	—
Skin changes	25 (6.3)	4 (1.0)	—	—
Vomiting	40 (10.2)	5 (1.2)	—	—
Decreased white cell count	11 (2.8)	1 (0.25)	—	—

The percentage is calculated out of the 394, the total number of patients in the study's cohort. Adverse effects are listed which occurred in more than 10 patients and with at least one reported grade 3–5 event.

Two patients died during study treatment (within 30 days after the last lenograstim administration): one patient with gastric cancer treated with docetaxel/cisplatin/5-flurouracil died from embolism considered not related to lenograstim and chemotherapy. The patient was diagnosed with a massive deep vein thrombosis (DVT) in the left arm involving the jugular, axillary, subclavian, and brachial veins. This extensive DVT caused an embolism. The investigator gave the following explanations as possible causes for the SAE: recent insertion of a port and paraneoplastic syndrome. Causality is sometimes difficult to determine, and it is reported according to the treating physician's impression on causality. One patient with prostate cancer treated with docetaxel single agent died from intracranial hemorrhage considered as related to lenograstim and chemotherapy.

3.4. Chemotherapy Treatment Delays, Changes, and Withdrawals. 85 (21.6%) patients were reported to have had at least one treatment delay in their chemotherapy regimen during the course of the study. The most common reason was neutropenia, with an incidence of 8.1%. Delay due to FN was reported in 0.5% of patients. When considering dose changes in chemotherapy treatment, a similar pattern was observed in the 144 (36.5%) patients who had at least one modification made to their chemotherapy dose during the study (Table 4).

Out of the 80 (20.3%) patients who did not complete their prescribed regimen, most withdrawals were due to disease progression, withdrawing consent from the study, and adverse events other than neutropenia, FN, asthenia, anorexia, myalgia, oral mucositis, or nail changes. Among the 13 patients who did not complete planned treatment due to death, 2 occurred within 30 days after last lenograstim administration. 21 patients (5.3%) of the total cohort had lenograstim-associated reasons for discontinuing treatment, with one death but a low incidence of adverse events and no toxicities (Tables 5 and 6).

3.5. Neutropenia-Associated Complications. Other secondary outcome measures included recording the number of infections, use of anti-infectives, and hospitalization associated

Table 4: Reasons for docetaxel-based chemotherapy dose delays and changes.

Reason	Number (%) of patients with ≥1 treatment delay	Number (%) of patients with ≥1 dose change
Amount of patients with at least one dose delay/change	85 (21.6)	144 (36.5)
Febrile neutropenia	2 (0.5)	4 (1.0)
Neutropenia	32 (8.1)	32 (8.1)
Anemia	1 (0.25)	9 (2.3)
Myalgia	1 (0.25)	8 (2.0)
Asthenia	2 (0.5)	6 (1.5)
Oral mucositis	—	4 (1.0)
Nail ridging	—	1 (0.25)
Infection (other than febrile neutropenia)	11 (2.8)	4 (1.0)
Other adverse events	8 (2.0)	22 (5.6)
Patient's personal convenience	17 (4.3)	—
Medical funder/insurance related	11 (2.8)	4 (1.0)
Other	12 (3.0)	90 (22.8)

The percentage is calculated out of the 394, the total number of patients in the study's cohort. A patient may have more than one reason recorded for change or delay in treatment.

Table 5: Reasons for discontinuing treatment.

Assessment	Number (%) of patients
Completion of the regimen prescribed	
Yes	314 (79.7)
No	80 (20.3)
Total	**394 (100)**
Reason why prescribed regimen* was not completed (if applicable)	
Disease progression	16 (4.1)
Patient withdrew consent from study (will continue chemotherapy)	16 (4.1)
Patient withdrew consent from study (no further chemotherapy)	5 (1.2)
Adverse experience (excluding toxicities**)	17 (4.3)
Toxicities**	0 (0.0)
Death	13 (3.3)
Other***	13 (3.3)
For some patients, reason listed above was linked to docetaxel or lenograstim	
Docetaxel related	23 (5.8)
Lenograstim related	21 (5.3)
Reasons for lenograstim-related withdrawal:	
Patient withdrew consent from study (will continue chemotherapy)	11 (2.8)
Patient withdrew consent from study (no further chemotherapy)	1 (0.0)
Adverse experience (excluding toxicities**)	6 (1.5)
Toxicity**	0 (0.0)
Death	1 (0.0)
Other	2 (0.0)

The percentage is calculated out of the 394, the total number of patients in the study's cohort.
*Docetaxel-based regimen or lenograstim.
**Toxicities: as specified according to the secondary objectives of the study: neutropenia, asthenia, anemia, anorexia, myalgia, oral mucositis, and nail changes.
***Other: medical funder related (4), investigator's decision (5), protocol violation (2), treatment delay due to hospitalization (1), and affordability (1).

Table 6: Causes of death in 13 patients.

Cause	Number of patients
Disease progression	5
Embolism*	1
Intracranial hemorrhage*	1
Multiple organ failure	1
Pleural infusion	1
Septic shock	1
Airway obstruction	1
Pneumonia	1
Unknown	1

*Within 30 days after last lenograstim administration.

with neutropenia. It was noted that 37 (9.4%) patients received anti-infective medication associated with neutropenia, while 5 (1.3%) patients received such medication for FN. Of these patients, 7 (1.8%) experienced at least one infection associated with grade 3 or 4 neutropenia. At least one hospitalization was required in 21 (5.3%) patients for neutropenia and 5 (1.3%) patients for FN.

4. Discussion

The primary outcome of the Granotax study found the incidence of clinically important grade 3-4 neutropenia to be 16.2% in adult patients being treated for a solid tumor with a docetaxel-based chemotherapy regimen and using lenograstim as primary prophylaxis. The study mainly included patients with breast cancer who were indicated for adjuvant therapy. In the BCIRG001 study conducted in 1491 women with node-positive breast cancer patients treated with adjuvant TAC versus FAC without the use of primary prophylactic G-CSF, the incidence of grade 3 or 4 neutropenia was 65.5% and the incidence of febrile neutropenia was 24.7% in treatment group treated with TAC [15]. Another study conducted in 1059 patients with high risk node-negative breast cancer showed that the addition of primary prophylactic granulocyte-colony stimulating factor in breast cancer patients treated with docetaxel, doxorubicin, and cyclophosphamide (TAC) decreased the incidence of neutropenic fever from 27.2% to 7.5% [12]. The present study's results thus clearly show a relatively low incidence of febrile neutropenia.

It could be argued that since this is not a systematic clinical trial but rather a study in real-life clinical settings, where monitoring is carried out according to the physician's normal practices, this low incidence of isolated neutropenia could not only be due to lenograstim use, but also be influenced by the lack of rigidly scheduled weekly tests leading to underreporting of neutropenia. However, more clinically important is the incidence of complicated neutropenia, where diagnosis is based on symptomatic presentation rather than requiring systematic hematological testing. In the Granotax study, FN was reported in 1.5% of patients and neutropenic infections in 1.8% of patients, rates far below the 30–40% incidence rate of complicated neutropenia usually reported with docetaxel-based chemotherapy regimens [13]. For example, a multicenter phase III study on 528 high risk node-negative breast cancer patients treated with adjuvant docetaxel-based regimen showed a reduced FN incidence rate from 27%, where only some patients were treated with reactive G-CSF (filgrastim or lenograstim) prophylaxis, to 7.5% with G-CSF primary prophylaxis for all patients [12]. The even lower rate in the present study may be due to a more widespread variability of baseline cancer grades and types. This study also showed a reduced incidence of nonneutropenia adverse events (secondary efficacy outcomes) with primary lenograstim prophylaxis, supporting earlier studies also showing reductions with G-CSFs [12].

An important result in the Granotax study was that neutropenia was the number one cause of chemotherapy treatment changes and delays, at a rate of 8.1% for each measure. Yet this is a relatively low rate when considering the results of a recent meta-analysis, which cites significant dose reductions and delays as common clinical practice in the management of patients with primary breast cancer, where febrile neutropenia and changes in liver enzymes were the major causes for dose reductions and delays [16]. An even more alarming picture might be observed in patients with metastatic breast cancer, where dose delays and reductions are common methods of reducing the toxicity and maintaining the quality of life but reduce overall survival [16]. It follows that the use of prophylactic lenograstim not only may increase the patient's exposure to the chemotherapy and allow for optimal dosing and duration of treatment, but also have an impact on important patient outcomes.

In the Granotax study, a total of 68 patients (17.3%) were reported to have experienced at least one grade 3-4 adverse event during the study, and 1 (0.25%) died from intracranial hemorrhage considered as related to chemotherapy and lenograstim. Only 4.3% of patients withdrew from treatment due to adverse events. Moreover, not one of these withdrawals was due to isolated or complicated neutropenia, despite a hospitalization rate of 5.3% for isolated neutropenia and 1.3% for complicated neutropenia. Overall, the rate of treatment withdrawals was 20%. Only 1.5% of patients withdrew treatment due to lenograstim related adverse events. This suggests good tolerability to lenograstim.

5. Overall Conclusion

The low incidence of isolated and complicated neutropenia reported in Granotax study may indicate support for the routine use of G-CSFs, such as lenograstim, in cancer patients on a docetaxel-based regimen. The Granotax study also confirms the safety of lenograstim in South African patients. The results from the Granotax study are hoped to contribute to the rational and appropriate use of G-CSF as primary prophylaxis in patients being treated with a docetaxel-based chemotherapy regimen in South Africa.

Conflict of Interests

Dr. Rashem Mothilal is the Medical Director of Sanofi South Africa. Dr. Alicia McMaster is the Medical Advisor for

oncology at Sanofi South Africa. The other authors declared no conflict of interests.

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