ARTÍCULOS ORIGINALES

Efficacy and safety of ior® LeukoCIM (G-CSF) in patients with neutropenia after chemotherapy

Eficacia y seguridad del ior® LeukoCIM (FEC-G) en pacientes con neutropenia posquimioterapia

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ABSTRACT

Neutropenia and infections are the most restrictive side effects during chemotherapy application. The granulocytic colonies stimulating factor activates the neutrophils, shortens the neutropenic period and can be effective against the potential risk of infection. The purpose of this study was to evaluate the efficacy and safety of LeukoCIM® (CIMAB, Havana). A retrospective observational study was carried out with data from the patients with neutropenic episodes enrolled in the open-label, non-randomized, multicenter, phase IV clinical trial. These patients were from *Gustavo Aldereguía Lima* hospital. They had been evaluated for one year. Demographic information, clinical data and side effects were analyzed. As prophylaxis indication LeukoCIM® was administrated 24-72 h after the last chemotherapy dose and as treatment when neutropenia was diagnosed. In both cases, a daily single 300 µg dose was administrated subcutaneously. The

application of the next chemotherapy cycle on time was the main variable of response and the product safety was assessed by measuring the side effects. Forty seven patients with 95 neutropenic episodes were enrolled. The 82.1 % of episodes received their next chemotherapy cycle on time. The most frequent side effects were: bone pain and fever (11.2 % respectively), hyperuricemia (9.2 %), leukocytosis and neutrophilia (7.1 %) and increased LDH (6.1 %). LeukoCIM® was effective in patients receiving chemotherapy, because it accelerated neutrophil recovery, decreased the incidence of febrile neutropenia and improved delivery of protocol doses of chemotherapy on time. Additionally, this product was considered safe for the studied patients since just known adverse events were reported.

Key words: Neutropenia, neutrophils, hematologic diseases, side effects, clinical trials.

RESUMEN

La neutropenia y las infecciones constituyen los eventos adversos más limitantes en la aplicación de quimioterapia. Los factores estimulantes de colonias de granulocitos activan los neutrófilos, acortan el periodo neutropénico y pueden ser efectivos contra los riesgos potenciales de infección. El propósito de este estudio fue evaluar la efectividad y seguridad del LeukoCIM® (CIMAB, La Habana). Se realizó un estudio retrospectivo, observacional con los datos de los pacientes incluidos en el ensayo clínico fase IV abierto, no aleatorizado y multicéntrico. Estos pacientes provenían del Hospital Gustavo Aldereguía Lima y se evaluaron durante un año. Se analizaron los datos demográficos, clínicos y de seguridad. Como profilaxis el fármaco fue administrado de 24-72 h después de la última dosis de quimioterapia y como tratamiento cuando la neutropenia había sido diagnosticada. En ambos casos la dosis única diaria fue de 300 µg por vía subcutánea. La administración del próximo ciclo de quimioterapia en tiempo resultó la variable principal de respuesta y la seguridad del producto se evaluó midiendo los eventos adversos. Se incluyeron 47 pacientes con 95 episodios neutropénicos. El 82,1 % de episodios recibió su próximo ciclo de quimioterapia en tiempo. Los eventos adversos más frecuentes fueron: dolor óseo y fiebre (11,22 % respectivamente), hiperuricemia (9,2 %), leucocitosis y neutrofilia (7,1 %) e incremento de LDH (6, 1%). LeukoCIM® resultó efectivo, pues aceleró la recuperación del número de neutrófilos, disminuyó la incidencia de neutropenia febril y permitió administrar las dosis de quimioterapia en tiempo según el protocolo. También se consideró seguro en la serie estudiada, pues solo reportó eventos adversos conocidos.

Palabras clave: Neutropenia, neutrófilos, enfermedades hematológicas, eventos adversos, ensayos clínicos.

INTRODUCTION

At the present, the treatment of cancer is based in the antineoplastic chemotherapy. One of the main side effects of chemotherapy drugs is a reduction in the number of neutrophils. This makes the body less able to fight against infection. There is a risk that the patient could develop a serious infection, which might have to be treated in hospital.[1-8] Myelosuppression, particularly neutropenia,

represents the major dose-limiting toxicity of systemic cancer chemotherapy. Importantly, studies in early stage of breast cancer and Non-Hodgkin Lymphoma (NHL) showed that severe and febrile neutropenia are the major causes of chemotherapy dose reductions and delays that reduce relative dose intensity and thus reduce the potential for prolonged disease-free and overall survival.[9] Researchers from the University of Rochester, the University of Washington and Duke University have concluded that the prophylactic use of granulocyte-colony stimulating factor (G-CSF) reduces febrile neutropenia and early deaths due to infections in adult patients receiving chemotherapy.[10]

Endogenous granulocyte colony-stimulating factor is a lineage-restricted colony-stimulating factor that principally affects the proliferation, differentiation, and activation of committed progenitor cells of the neutrophil-granulocyte linage. In addition, endogenous G-CSF enhances certain functions of mature neutrophils, including phagocytosis, chemotaxis, and antibody-dependent cellular cytotoxicity. It is an 18 000 Dalton glycoprotein produced by monocytes, fibroblasts, and endothelial cells. G-CSF has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of other hematopoietic cell types.[11-17] G-CSF is also known as colony-stimulating factor 3 (CSF 3).

The administration of prophylactic G-CSF formulations to patients receiving chemotherapy accelerates neutrophil recovery, decreases the incidence of febrile neutropenia and improves delivery of protocol doses of chemotherapy.[10,18-26] Chemotherapy can cause myelosuppression and unacceptably low levels of white blood cells, making patients prone to infections and sepsis.[1-2,27]

Researchers from Poland and Germany reported that adding Neupogen® (Filgrastim) or Granocyte® (Lenograstim) reduced the incidence of neutropenic fever and other symptoms associated with Taxotere® (docetaxel), Adriamycin® (doxorubicin) and Cytoxan® (cyclophosphamide) (TAC). The addition of Neupogen® or Granocyte® reduced the percentage of patients with clinically relevant symptoms from 64 to 46 %.[28]

The American Society of Clinical Oncology (ASCO) reports yearly the results of different investigations about the use hematopoietic colony-stimulating factors. ASCO convened an Update Committee composed of the original Expert Panel and select ad hoc members to present the 2006 evidence-based clinical practice guideline update for the use of these kinds of drugs. The Expert Panel listed three reasons to value the use of the G-CSF in neutropenic patients.[29]

1. Therapeutic intervention with CSF can help reduce the incidence of infectious episodes and infection-related morbidity and mortality.

2. CSF could be used to shorten the neutropenic period.

3. It is recommended in patients with mielotoxicity, pneumonitis and mucositis, due to chemotherapy or radiotherapy.

The safety of the different colony stimulating factor was studied in many investigations. The more common side effects are: bone pain, injection site pain, headache, arthralgia, myalgia, back pain,[6,30] fever, chills, body aches, flu symptoms, nausea, vomiting, loss of appetite, diarrhea, constipation, hair loss, itchy skin.[5-7,30-36]

One or more of the following signs and symptoms were observed shortly after the subcutaneous injection of G-CSF in patients with chronic myeloid leukemia

undergoing allogeneic peripheral blood stem cell transplantation: dyspnea, chest pain, nausea, hypoxemia, diaphoresis, anaphylaxis, syncope and flushing.[33]

A new recombinant G-CSF preparation was recently obtained by recombinant DNA technology. It is a highly purified methionyl form of *E. coli* expressed recombinant human G-CSF containing 175 amino acid residues that was developed by the Center of Molecular Immunology (CIM, Havana, Cuba, and is currently marketed by CIMAB.SA.[37,38]

LeukoCIM® regulates the production and release of functional neutrophils from the bone marrow and controls their proliferation, differentiation and other cellular functions. LeukoCIM® results in a dose dependent increase in neutrophil counts which return to baseline within 4 days of discontinuation of it. This product is used in the treatment of patients with neutropenia due to chemotherapy.[38]

According to *Ducongé* et al., LeukoCIM®, is pharmacokinetic comparability with Neupogen®, Hoffman-La Roche, licensed by Amgen.[37]

This paper is about the efficacy and safety of ior® LeukoCIM in primary or secondary prophylaxis or treatment in neutropenic patients.

METHOD

A phase IV, open-label, non-randomized, multicenter clinical trial was carried out in neutropenic patients due to chemo/radiation antineoplastic therapy.

Sample size

The number of subjects to the clinical trial was calculated stratified as follows:

Primary prophylaxis: Hypothesis: To increase the value of ANC≥ 1.5 x 10^9/ L in the 75 % of the patients. Assuming error type I (α= 0,05) and error type II (β= 0,2) with 85 % of reference, in order to answer the hypothesis, it needs 91 patients and taking to account 10 % of losing the final number was 101 patients.

Secondary prophylaxis: Hypothesis: To increase the value of ANC≥ 1.5 x 10^9/L in the 65 % of the patients. Assuming error type I (α= 0,05) and error type II (β= 0,2) with 75 % of reference, in order to answer the hypothesis, it needs 125 patients and taking to account 10 % of losing the final number was 138 patients.

Treatment: Hypothesis: To increase the value of ANC≥ 1.5 x 10^9/L in the 80 % of the patients. Assuming error type I (α= 0.05) and error type II (β= 0.2) with 70 % of reference, in order to answer the hypothesis, it needs 119 patients and taking to account 10 % of losing the final number was 133 patients.

The total number of sample size for the clinical trial was 372 patients, but we used in this work the subset of patients included in the "Dr. Gustavo Aldereguía Lima" University Hospital.

From it, 95 neutropenic episodes were studied picked up in clinical records and Case Report Forms (CRF) belonging to the all the patients (47) treated in the "Dr. Gustavo Aldereguía Lima" University Hospital, Cienfuegos during one year. With this data a retrospective observational descriptive study was carried out. The following variables were analyzed: age, gender, ethnicity, indication for G-CSF

administration, values of absolute neutrophil count (ANC), and the value of uric acid, the number of doses administered, the regimen of treatment and the interruption of treatment.

The protocol was approved according to International Conference Harmonization (ICH) by the Institutional Review Board (IRB) of the "Dr. Gustavo Aldereguía Lima" University Hospital, Havana, and by the Cuban Regulatory Authority. The informed consent to participate, were included and all patients singed it.

Also, the side effects were analyzed. They were classified according to WHO Toxicity Criteria[18,39] and their relation of causality was classified according to Karch Lasagna algorithm.[40]

G-CSF formulation

LeukoCIM®, has been produced following the standard of quality for injectable formulations, TRS 823 and 822 GMP regulations for pharmaceutical and biological drug products, respectively; and also following the Cuban norm 16/2000 from CECMED, Havana, Cuba (i.e. The Cuban Regulatory Agency identified as The State Center for Drug Quality Control).[37] Each vial contains 300 (G30) mg/mL (specific activity: 108 UI/mg proteins) of sterile recombinant human G-CSF, 50 mg sorbitol, 0.04 mg polysorbate 80, 0.59 mg sodium acetate and water for injection to complete 1 mL.[38]

LeukoCIM® was administrated in primary/secondary prophylaxis by subcutaneous way in the deltoid region 24-72 h after the last chemotherapy dose during 7-10 days according investigator´s criteria. The daily single dose was 300 µg.[38]

Its use as treatment in patients with febrile neutropenia (ANC≤ 1 x 10^9/L) or non febrile neutropenic (ANC≤ 0.5 x 10^9/L) until ANC at least 2-3 x10^9/L. The daily single dose was 300 µg by subcutaneous way in deltoid region.[38]

The administration of the next chemotherapy or radiation therapy cycle on time was the main variable of response. The value of ANC and time to absolute neutrophil count recovery were also evaluated.

The results were introduced in a data base and they were analyzed by SPSS version 13.0 for windows used descriptive statistical and they were express in number and percent. Mean, minimum and maximum values were determinate. Also Pearson λ^2 Test was determinate to the main variable of response.

RESULTS

Forty seven patients with 95 neutropenic episodes were enrolled. Twenty eight patients (59.6 %) had one neutropenic episode, seven patients (14.9 %) had three episodes, five patients (10.6 %) had two episodes, four patients (8.5 %) had four episodes, with five, seven and eight episodes had one patient (2.1 %) respectively. In the 8.4 % (eight patients) of the episodes the indication was noted as primary prophylaxis, in 31.6 % of episodes (thirty patients) as secondary and in 60% of episodes (fifty seven patients) as treatment.

The median age of the patients was 52 years. There were 29 females (62 %) and 18 males (38 %). White skin was the predominant color (77.9 %), followed by brown (12.6 %) and black (9.5 %). The more common patient's diagnoses by

neutropenic episodes were: acute non-lymphoid leukemia (34.7 %), non-Hodgkin's lymphoma (15.8 %) and Hodgkin's lymphoma (13.7 %) (table 1).

Table 1. Distribution of episodes by patient's diagnoses and indication

Patient's diagnoses	Prophylaxis No. episodes	Treatment No. episodes	Total episodes
Acute non-lymphoid leukemia	9	24	33
Acute lymphoid leukemia	0	3	3
Leukemia biphenotypic acute	0	2	2
Non-Hodgkin's lymphoma	5	10	15
Hodgkin's lymphoma	7	6	13
Multiple myeloma	1	0	1
Myelodysplastic syndrome	7	1	8
Breast carcinoma	6	4	10
Ovarian adenocarcinoma	3	4	7
Laryngeal carcinoma	0	1	1
Epidermoide lung carcinoma	0	1	1
Rectus carcinoma	0	1	1
Total	38	57	95

Source: Clinical records and CRF from: An open-label, no-randomized, multicenter, phase IV clinical trial "Efficacy and safety of LeukoCIM® in neutropenia post chemotherapy". Gustavo Aldereguía University Hospital, Cienfuegos, Cuba. 2007.

The initial mean uric acid level was 266.34 and the final was 309.87.

In 9 episodes there was interruption of treatment (9.5 %). Fifty and half percent received the treatment in ambulatory way (48 episodes), whereas 48.4 % was hospitalized (47 episodes).

From 38 patients that were enrolled in the prophylaxis stratus, 32 received their next chemotherapy cycle on time (84.2 %). In the other hand, from 57 episodes included in the treatment stratus, 46 received their next chemotherapy cycle on time (80.7 %) (table 2). According to Pearson λ^2 Test, there was no association between the main variable of response and the stratus p= 0.662.

Table 2. Distribution of episodes by indication vs. the main variable of response

Next chemotherapy cycle on time?	Indication		Total	%
	Prophylaxis	Treatment		
	No. (%)	No. (%)		
Yes	32 (84.2%)*	46 (80.7%)*	78	82.1
No	6 (15.8%)	11 (19.3%)	17	17.9
Total	38	57	95	100

* Pearson λ^2 p= 0.662.

Source: Clinical records and CRF from: An open-label, no-randomized, multicenter, phase IV clinical trial "Efficacy and safety of LeukoCIM® in neutropenia post chemotherapy". Gustavo Aldereguía University Hospital, Cienfuegos, Cuba. 2007.

About the seventeen patients that no received their next chemotherapy cycle on time, 2.1 % was due to prolonged neutropenia, thrombocytopenia and pneumonia respectively, 8.4 % because of death and 3.1 % due to withdrawal (table 3).

Table 3. Distribution of episodes by indication *vs.*, cause of delaying chemotherapy cycle

Cause of delaying chemotherapy cycle	Indication		Total	
	Prophylaxis	Treatment		
	No.	No.	No.	%
Prolonged neutropenia	0	2	2	2.1
Death	0	8	8	8.4
Withdraw	3	0	3	3.1
Pneumonia	1	1	2	2.1
Thrombocytopenia	1	1	2	2.1
Total	5	12	17	17.8

Source: Clinical records and CRF from: An open-label, no-randomized, multicenter, phase IV clinical trial "Efficacy and safety of LeukoCIM® in neutropenia post chemotherapy". Gustavo Aldereguía University Hospital, Cienfuegos, Cuba. 2007.

The initial mean value of ANC was 1.49 cells/L and the final was 5.51 cells/L.

The mean dose number administered to obtain the recovery of absolute neutrophil count was 6.69, so the recovery of ANC was approximately in a week; therefore the majority of the patients received their next chemotherapy cycle on time (82.1 %) (table 2). The final value of the ANC allowed measuring the main variable of response.

About the safety of the LeukoCIM®, from 95 neutropenic episodes, 55 involved side effects (58 %) there were distributed in 28 patients (59.6 %). These adverse events were distributed as follows: with 1 event 32.6 % of episodes; 2 events 18.9 % of episodes; 3 events 2.1 % of episodes; 4 events 1.0 % of episodes; 6 events 2.1 % of episodes; and 8 events 1.0% of episodes (table 4).

Table 4. Number of side effects by neutropenic episodes and patients

Side effects No.	Episodes No.	%	Patients No.	%
1	31	32.63	14	29.78
2	18	18.94	7	14.89
3	2	2.10	1	2.12
4	1	1.05	3	6.38
6	2	2.10	1	2.12
8	1	1.05	2	4.25
Total	55	100	28	100

Source: Clinical records and CRF from: An open-label, no-randomized, multicenter, phase IV clinical trial "Efficacy and safety of LeukoCIM® in neutropenia post chemotherapy". Gustavo Aldereguía University Hospital, Cienfuegos, Cuba. 2007.

Relating to toxicity of the product, 74 episodes (75.5 %) had mild intensity, 13 (13.3 %) were moderate, 8 (8.1 %) were classified as grave and 3 (3.1 %) were severe. Concerning to the relation of causality between LeukoCIM® and side effects,

60 episodes (61.2 %) were classified as possible, 24 (24.5 %) were probable, 11 (11.2 %) were very probable and 3 (3.1 %) were classified as remote.

Eight patients died, this was classified grave and possible due to their illness and not because of the used of LeukoCIM®.

LeukoCIM® was generally well tolerated, and only rarely were the adverse effects severe enough to require discontinuation of the treatment.

The side effects reported most frequently were: bone pain and fever 11 episodes (11.2 % respectively), hyperuricemia 9 episodes (9.2 %), leukocytosis and neutrophilia 7 episodes (7.1 %), increased of Lactate dehydrogenase (LDH) 6 episodes (6.1 %), thrombocytopenia 5 episodes (5.1 %), headache and nauseas 4 episodes (4.1 %) respectively, hypotension 3 episodes (3.1%), injection site pain, asthenia, myalgia and anorexia 2 episodes (2.0 %) each one. The other side effects such as: vomiting, retinal hemorrhage, upper digestive bleeding, itchy skin, melena, epistaxis, pruritus, chills, renal insufficiency, weight loss, eritema, drowsiness, transpiration skin, cellulitis and increased of leukocyte alkaline phosphatase (LAP) 1 episode (1.0 %) each one (table 5).

Table 5. Side effects

Side effects	Prophylaxis No.	Treatment No.	Total	%
Bone pain	5	6	11	11.22
Fever	8	3	11	11.22
Hyperuricemia	4	5	9	9.18
Death	0	8	8	8.16
Leukocytosis	4	3	7	7.14
Neutrophilia	4	3	7	7.14
Increased of LDH	4	2	6	6.12
Trombocytopenia	4	1	5	5.10
Nauseas	0	4	4	4.08
Headache	0	4	4	4.08
Hypotension	3	0	3	3.06
Injection site pain	0	2	2	2.04
Asthenia	2	0	2	2.04
Myalgia	2	0	2	2.04
Anorexia	0	2	2	2.04
Vomiting	0	1	1	1.02
Retinal hemorrhage	0	1	1	1.02
Upper digestive bleeding	0	1	1	1.02
Itchy skin	1	0	1	1.02
Melena	0	1	1	1.02
Epistaxis	0	1	1	1.02

Pruritis	1	0	1	1.02
Chills	1	0	1	1.02
Renal insufficiency	0	1	1	1.02
Weight loss	1	0	1	1.02
Erythema	1	0	1	1.02
Drowsiness	1	0	1	1.02
Transpiration skin	1	0	1	1.02
Cellulitis	0	1	1	1.02
Increased of LAP	1	0	1	1.02
Total	48	50	98	100

Source: Clinical records and CRF from: An open-label, no-randomized, multicenter, phase IV clinical trial "Efficacy and safety of LeukoCIM® in neutropenia post chemotherapy". Gustavo Aldereguía University Hospital, Cienfuegos, Cuba. 2007.

Thirteen episodes (13.6 %) received concomitant treatment. The more common drugs were: acetaminophen and dipirona in order to treat fever, chills, headache and bone pain, gentamicin to treat sepsis and cytotoxic anticancer agents such as: andriamycin, mitoxantrone and cytosine arabinosid.

DISCUSSION

The use of LeukoCIM® has permitted the administration of an effective dose of chemotherapy and the majority of the patients received the next cycle on time, so the product was effective as other G-CSFs.[9,10,28] Its pharmacokinetic is comparability with Neupogen®,[37] also the study with a glycosylated CHO-derived G-CSF has reported that the bioavailabilities of different G-CSF molecular forms are similar.[41]

Data on the safety of the treatment with G-CSF formulations have been reported with standard doses of chemotherapy or high doses with or without hematopoietic progenitor's transplant.[32,34,36,42-46]

In our study, the levels of the uric acid were monitored before and after the use of the LeukoCIM®, hyperuricemia was detected in the 9.18 % of episodes. These spontaneously reversible elevations in uric acid were generally mild to moderate. At the end of the treatment the patients recovered their normal uric acid value in a week, this agrees with the clinical trial carried out with *Wilford* et al.[38] and with the literature consulted.[34,47]

The bone pain was manifested frequently. LeukoCIM®-induced bone pain usually can be effectively prevented or treated with non-opioid oral analgesics (e.g. acetaminophen).[5-7,46] In severe cases, opioid analgesics may be use.[47] This result agrees with clinical studies reviewed, which have shown good profile of security and tolerance for LeukoCIM®[38] and others G-CSFs;[10,45,46] according to these reviews bone pain mild-moderate 10 %, bone pain severe 5 % and local reactions on injection site 2-5 % in patients treated with subcutaneousinjection.[24,48] Other side effects like: fever, neutrophilia, leukocytosis, increased of LDH, erythema, chills, itchy skin, hypotension and thrombocytopenia are also reported in literature.[5-7] It

could be prescribe painkillers such as acetaminophen to help reduce temperature and prevent chills.[5-7,31]

Besides that, another side effects as difficulty breathing, sudden or severe pain in the left upper stomach spreading up to the shoulder, constipation, diarrhea, hair loss, white patches or scores inside the mouth or on the lips and dysuria have been reported,[5-7,31] also chest pain, hypoxemia, diaphoresis, anaphylaxis, syncope and flushing[33] but not in this study.

In our study, transient decreases in blood pressure (< 90/60 mmHg), which did not require clinical treatment, was reported in 3 cases.

The increased in neutrophil counts during mobilization, consistent with the biological effects of LeukoCIM® and no sequelae were associated with any grade of leukocytosis.

About renal insufficiency, the relationship of this event to LeukoCIM® remains unclear since it occurred in patient with culture-proven infection with clinical sepsis who was receiving potentially nephrotoxic antibacterial therapy (Gentamicin).

One patient, with acute non-lymphoid leukemia, had retinal hemorrhage and upper digestive bleeding during thrombocytopenia due to myeloablative therapy. In relation to the eight dead patients, they died because their illness and not because of LeukoCIM® as we can confirm according to the necropsy results. Four patients died because Bacterial bronchopneumonia (direct cause) and Non-Hodgkin's lymphoma (basic cause). Three patients died because bilateral bronchopneumonia (direct cause) and acute non-lymphoid leukemia (basic cause). One patient died because acute respiratory insufficiency (direct cause) and multiple myeloma (basic cause).

These results agree with the literature consulted, up to the moment any death has been related to G-CSF used.[5-7,31,33]

No evidence of interaction by LeukoCIM® with other drugs was observed in the course of clinical trial. The patients received in addition to LeukoCIM®: acetaminophen, dipirona, gentamicin and cytotoxic anticancer agents (andriamycin, mitoxantrone and cytosine arabinosid). According to the literature consulted the administration of Molgramostim (Growgen®) with cytotoxic and antiretroviral agents could produced thrombocytopenia[49,50] and Filgrastim with lithium could produce leukocytosis.[51,52]

CONCLUSIONS

These data document the benefits of G-CSF in adult cancer patients receiving chemotherapy.

LeukoCIM® was effective to patients receiving chemotherapy, because accelerates neutrophil recovery, decreases the incidence of febrile neutropenia and improves delivery of protocol doses of chemotherapy on time. Also its use was safe in the studied patients, because it reported known adverse effects.

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