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SINGLE DOSE FILGASTRIM IN CYTOTOXIC-INDUCED NEUTROPAENIA IN CHILDREN
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ABSTRACT

Objective: **To document the impact of fixed dose weight adjusted filgastrim (G-CSF) in cytotoxic-induced neutropaenia.**
Design: **A descriptive cross-sectional study.**
Setting: **Paediatric Oncology Unit at Kenyatta National Hospital, Nairobi, Kenya.**
Subjects: **All paediatric oncology patients who had developed cytotoxic-induced neutropaenia.**
Main outcome measures: **The following were documented for every tissue proven case of malignancy; age, sex, type of malignancy, treatment regimen and schedule, initial blood count at the time of neutropaenia; subsequent blood counts daily for five days from day one of single dose filgastrim, and the calculated neutrophil incremental count.**
Results: **Initially eight patients with solid tumours previously treated with filgastrim revealed that cytotoxic induced neutropaenia could be ameliorated by a single dose of filgastrim. Subsequently, the study listed thirty patients. This cohort consisted of; 37% rhabdomyosarcoma, 30% Burkitts, 27% acute lymphoblastic leukaemia and 6% Hodgkin's lymphoma. Increased neutrophil count after 48 hours was documented in 26 (87%) patients, with absolute neutrophil counts range of 0.5 to 31.5 x $10^9/_L$. This response was significantly influenced by gender (p>0.0001), malignancy type and chemotherapy regimen (p>0.001).**
Conclusion: **The study shows that chemotherapy induced neutropaenia can be alleviated by a single dose of filgastrim without adverse effects on lymphoblastic leukaemia. This study suggests that a single dose of filgastrim should be first tried in cytotoxic induced neutropaenia in the paediatric age group.**

INTRODUCTION

Filgastrim, one of the colony stimulating factors has been used variedly in terms of doses, duration and setting of leucopaenia. This is because colony stimulating factors (G-CSF and GM-CSF) which are glycoproteins, act on haematopoietic cells to stimulate proliferation, differentiation commitment and some end-cell functional activation(1). G-CSF filgastrim regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation. The latter includes enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing and the increased expression of some functions associated with cell surface antigens (2). Among these growth modifiers G-CSF use in drug induced neutropenia is better understood and established (3). This is particularly so because neutropaenia is a frequent complication of cancer chemotherapy as cytotoxic agents interfere with the generative capacity of cells (4). Furthermore chemotherapy drugs also affect 'healthy' cells thereby damaging their regenerative capability (5). Rapidly dividing cells like those of the bone marrow are most affected leading to neutropaenia as well as other adverse events associated with chemotherapy such as gastrointestinal toxicity and alopecia. Following damage to the bone marrow cells, all progenitor cells are consequently impaired and a fall in absolute neutrophil count (ANC) levels ensues (6).

The magnitude of neutropaenia is directly related to the intensity of the chemotherapy regimen and it also determines the risk of initial infection and subsequent complications. A number of host and disease related factors influence the level of neutropenia (7,8).

Furthermore it is possible to use predictors of neutropenia which include an absolute lymphocyte count of less than 700/mm^3, a fall in haemoglobin or ANC during the first cycle of chemotherapy (9,10).

Complications of neutropaenia particularly due to malignancy and treatment include infections, morbidity and even mortality (10). Low neutrophil levels compromise a patient's defense system and cause increased vulnerability to potentially life-threatening infections. This is not just because of the absence of granulocytes but also due to the disruption of several barriers, integumentary, mucosal and mucociliary, and because of the inherent microbial floral shifts that accompany severe illness and antimicrobial usage (9). Subsequently treatment requires hospitalisation for intravenous antibiotics and/or anti-fungals which puts a burden on the time and resources of the healthcare provider (2). In such situations, use of colony stimulating factors can break this vicious cycle not just to ameliorate the neutropaenia, but even to reduce the incidence of febrile neutropenia (FN) by 50% and concomitant decrease of 35% of hospitalisation rates and 50% decrease of intravenous antibiotic requirement (11,12).

Colony stimulating factors have also been used after chemotherapy for myeloid and lymphoid haematological malignancies in adults divulging the feasibility and safety of the drug in this setting (13-15). In children, data reporting on similar malignancies have not indicated detrimental stimulation of tumour cells by these growth factors therefore its adoption in most paediatric oncology settings including the Kenyatta National Hospital (KNH) (16,17).

However, there are no guidelines for optimal G-CSF doses in peadiatrics (9). In resource restrictive settings the overall cost of using filgastrim may be prohibitive and requires evaluation for cost cutting measures. It is against this background that this study was set up to look back and document the impact of a single dose filgastrim in paediatric malignancies including acute lymphoblastic leukaemia (ALL) but excluding acute myeloid leukaemia.

MATERIALS AND METHODS

Study design and method: The data were collected in a retrospective manner in this descriptive cross-sectional three year hospital based study. Records of patients admitted into the Paediatric Oncology Unit (POU) of KNH were reviewed. Those who had tissue proof of malignancy and received cytotoxic drugs were evaluated. Case records of patients treated and on follow up between July 2000 to July 2003 were scrutinised for the study criteria. The study was designed to document the impact of fixed-dose, weight-adjusted filgastrim (G-CSF) in cytotoxic-induced neutropaenic patient. At the POU neutropaenic patients were to receive neupogen (filgastrim) whenever the netrophil count fell below 0.5x $10^9/_L$. Thirty oncology cases managed at the POU who had documented features of Grade 4 toxicity (Figure1) were evaluated. Each case had received a single dose of filgastrim 5μg/kg subcutaneously, absolute neutrophil counts before and daily for five days after the filgastrim administration had been recorded.

All the blood counts had been performed on an automated haematology counter (Coulter Counter model S). The peripheral blood film with manual differential white cell counts which had been performed by haematologists were reviewed by the investigator.

Inclusion criteria: All cases at the POU who had been on chemotherapy and developed Grade 4 neutropaenia according to World Health Organisation Toxicity Grading (Figure 1).

Exclusion criteria: Diagnosis of acute myeloid leukaemia, lack of sufficient documentation of the following features; tissue/histologic proof of diagnosis, ascertainment of grade 4 toxicity, duration of treatment with filgastrim and complications of neutropenia.

Measurable values: The main outcome measures required and documented in every case included age, sex, malignancy type, treatment regimen and schedule, initial blood counts on day of nadir neutropenia with absolute neutrophil counts (ANC), daily blood count for five days after dosing with filgastrim, with ANC and the calculated neutrophil increment.

Data analysis: Subsequently the data were screened, pooled and entered in the SPSS. Results presented as proportions, ratios, percentages, means, ranges, percentages and tables.

Ethical considerations: Strict confidentiality was observed in concealing the identities of the cases. Since this was a retrospective study it had no direct impact on the individual patients and had not influenced their management in any way. Furthermore, permission to publish the article was obtained from KNH.

RESULTS

Perusal of treatment records of the patients managed in the POU at the KNH in the period between 2000 and 2003, for the study criteria enlisted 30 cases. The characteristics of these cases were as follows: - Overall age range was between two years and thirteen years with a mean 8.6 (SD 8.6± 1.5) years, while 6-10 years was the mode.

Gender: Sex distribution showed that there were 13 (43%) males, 17 (57%) females and the male: female ratio was 1: 1.3.

Tissue/Histological types: The main type of malignancies in the study were rhabdomyosarcoma (37%), Burkitt's lymphoma (30%) and ALL (27%).

Cytotoxic drugs: Patients received different chemotherapy regimens as per schedule for the tissue type of malignancy though all combination included vincristine and adriamycin. The majority (77%) of drug complements included cyclophosphamide while 52% receiving in addition prednisone, and 27% cisplatin (Table 1).

Profile of white blood cells of the cases: The total white cell counts, before dosing with filgastrim, ranged between 0.3 and 2.5 x $10^9/_L$ while the range of ANC was 0.067 to 0.5 x $10^9/_L$ with a mean of 0.307x $10^9/_L$. Two days (48 hours) after the single dose of filgastrim, the total white cell count ranged between 0.6 and 32.1 X $10^9/_L$ while the ANC was between 0.497 and 31.458 x$10^9/_L$ with a mean of 5.68 x$10^9/_L$. This neutrophil increment was equivalent to 230% to 26,322% and a mean of 2,414%. This increment occurred within the first 48 hours for the majority 26(87%) of the patients, while four (13%) study subjects did not demonstrate any increment at this point in time (Table 2).

Table 1

Distribution of malignancies and the cytotoxic regimen given in the study cases

Malignancy	Frequency No.	(%)	Gender M	F	Age years Range	Mean	Regimen
Rhabdomyosarcoma	11	37	2	9	2-11	5.55	VAC-Cis
ALL	8	27	6	2	9-11	10.25	VAP/VAC
Burkitt's	9	30	4	5	5-9	7.67	CHOP
Hodgkin's	2	6	I	1	10-12	11	CHOPP

V = Vincristine, A & H Adriamycin, C=Cyclophosphamide, Cis= Cisplatin, P=Prednisone

Table 2

Chemotherapy regimen and neutrophil increment

Regimen	Gender M	F	Absolute neutrophil x $10^9/_L$ (nadir neutropenia) Mean	Range	Absolute neutrophil increment count x $10^9/_L$ Mean	Range	Average neutrophil increment %
VAC-Cis	0	8	0.364	0.18-0.49	4.257	1.302-7.520	1487
CHOP	5	5	0.284	0.12-0.5	8.016	0.497-26.322	5545
VAP	3	1	0.249	0.12-0.4	3.482	1.098-6.144	1377
CHOP + Procarbazine	1	1	0.368	0.28-0.45	9.230	8.284-10.235	2795
VAC	2	1	0.268	0.07-0.45	3.367	0.961-5.184	1371

V = Vincristine, A & H =Adriamycin, C= Cyclophosphamide, Cis= Cisplatin, P=Prednisone

The results showed that, the age of the patient did not seem to influence this neutrophil increment (Table 3) ($p>0.01$). Gender profile showed average neutrophil increments as follows; males 1975% and females 3549% showing that female subjects had a significantly higher increment than males ($p<0.001$). The most significant neutrophil increment (4129%) occurred in patients with Burkitts lymphoma who were on the CHOP regimen, followed by those with Hodgkin's lymphoma who were on CHOP with Procarbazine (3426%) while the least (771%) increment occurred in those patients on the VAP/ VAC and VAC-Cis regimen used in patients with ALL and rhabdomyosarcoma respectively. (Table 2 and 4). These differences are all statistically significant ($p<0.001$).

Figure 1
WHO Toxicity Grade

Toxicity Grade	Severity	ANC x $10^9/_L$
0	Mild	>2.0
1	Mild	1.5 - 1.9
2	Mild	1.0 - 1.4
3	Moderate	0.5 - 0.9
4	Severe	<0.5

Table 3
Age and neutrophil increment

Age group (years)	Average neutrophil increment (%)	
	Male	Female
0-5	1930	1489
6-10	2783	4669
11-15	1367	587

Table 4
Tumour type and neutrophil increment

Tumour type	Average neutrophil increment %
Rhabdomyosarcoma	771
ALL	916
Burkitt's lymphoma	4129
Hodgkin's lymphoma	3426

The four cases who did not demonstrate an increment at 48 hours were two males (aged 9 and 11 years) having acute lymphoblastic leukaemia and two females (aged 8 and 9 years), having rhabdomyosarcoma and Burkitt's lymphoma. One of the males had relapsed leukaemia while the other was in the intensification phase of cytotoxic drug treatment. Both females were getting the induction remission phase of treatment.

DISCUSSION

The results of this study compares well in many aspects with those that have employed the standard treatment of filgastrim schedule. There are however notable variations particularly in the patient characteristics, While the age range of 2 - 13 years and mean age of 8.6 years in this study is closely similar with results from other studies, the sex distribution is different as in the current study there were more females compared to the males with the male to female ratio of 1:1:3. In other studies males significantly exceeded females (17-20). Furthermore, the present study showed that the level of neutropaenia was not affected by the age of the patient. However, studies documenting changes in adults, have revealed that neutropenia inversely affects those over 65 years of age (3,4). These observations could be due to the fact that the marrow reserve and response to stress is known to be age dependent and is better in the younger than older age groups. There is also an apparent gender influence on the degree of increment of absolute neutrophil count. This study demonstrates that females demonstrate a greater increment compared to males. This is thought to be due to partly the male to female ratio which favours females and the fact that the most common malignancy in this study was rhabdomyosarcoma which was documented in more females than males. The other comparative studies include mainly cases of ALL and neuroblastoma, which appeared to be predominantly in males (14-18, 19,21). The three common malignancies in this study associated with neutropaenia were rhabdomyosarcoma, Burkitt's lymphoma and ALL. These would subsequently reflect the type of cytotoxic drug schedules used and associated with neutropaenia and does not reflect the most frequent malignancies seen at our POU. The frequency of paediatric malignancies at our POU has previously been documented and shows that the most common is Burkitt's lymphoma, followed by ALL and then Wilms' tumour and rhabdomysarcoma (20).

The cytotoxic drugs cisplatin and adriamycin in combination with other agents were found to be more likely to cause neutropenia than other combinations. This is consistent with the other findings of the type of treatment schedule resulting in neutropaenia that included cisplatin and adriamycin and in the VAC combination for solid tumours (18,19,21,25), (Table 3).

The highest average neutrophil increment was demonstrated from patients with Burkitt's lymphoma, followed by Hodgkin's lymphoma, both of whom received the CHOP and CHOPP regimen respectively (Table 4). The increment shown by this group of patients is about four times that recorded by those patients who were on the VAC-C is regimen (Table 2). In CHOP the myelotoxicity is attributed to adriamycin and cyclophosphamide, while in VAC-Cis, myelotoxicity is due to adriamycin actinomycin D, cyclophosphamide and more importantly, cisplatin. Procarbazine in CHOPP appears to be less myelotoxic compared to Cisplatin in VAC-Cis (22,23).

The current, study like others, showed that neutropenic patients show improved neutrophil counts (levels $\geq 2x10^9/_L$) on filgastrim (9,17,22,27). However four cases showed no response which is thought to be due to the level of myelotoxicity of the chemotherapeutic agents used (22,26). It is of note that the patients with acute lymphoblastic leukaemia who were on filgastrim did not respond adversely, for instance with emergence of blast cell in peripheral blood. This observation is consistent with those of other investigators (15-17). However the lower neutrophil increment noted could be due to poor bone marrow reserve after intensification of cytotoxics in the leukaemia cases. These patients were receiving intense chemotherapy (intensification phase) consisting of vincristine, cytosine arabinoside, adriamycin, cyclophosphamide and six mercaptoprine. This combination is generally associated with significant myelosuppression, necessitating the use of filgastrim, in the majority of cases (28).

In conclusion this study has shown that a single dose of filgastrim (G-GSF) alleviated chemotherapy induced neutropenia in most paediatric oncology patients. The absolute netropaenia observed in this study corresponded with grade 4 level according to the World Health Organisation (9) (Figure 1). This grade of neutropaenia makes interruption of the chemotherapy regimen necessary and the usual practice is that colony stimulating factors are given only at this level of neutropenia (14,17-19). Since a single dose filgastrim showed improvement it is presumed that in our setting it would be risky not to consider neutropaenia at or below grade 4 for intervention. In resource poor settings, a single dose of filgastrim should first be tried in the management of cytotoxic-induced neutropaenia.

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REFERENCES

1. Duhrsen, U., Villeval, J. L., Boyd, J., *et al.* Effects of combinant human granulocyte colony stimulating factor on haematopoietic progenitor cells in cancer patients. *Blood.* 1988; **72:**2074-2091.
2. Klatersky, J. Current attitudes for therapy of febrile neutropenia with consideration to cost-effectiveness. *Curr. Opin. Oncol.* 1998; **10:** 284 - 290.
3. Morrison, V., Picozzi V., Scott S. *et al.* The impact of age on delivered dose intensity and hospitalisations for febrile neutropenia in patients with intermediate-grade non - Hodgkin's lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. *Clin. Lymphoma.* 2001, **2:** 47 - 56.
4. Kuderer, N., Cosler, L., Crawford, J. *et al.* Cost and mortality associated with febrile neutropenia in adult cancer patients, *Proc. Am. Soc. Clin. Oncol.* 2002, **21:** 250a. Abstract 998.
5. Chen S., Zhang Z. and Liu J. A study of the effects of chemotherapy with or without G-CSF on neutrophil counts and serum G-CSF levels in leukemia patients, *Zhonghua Nei Ke Za Zhi.* 1996; **35:** 249-252.
6. Epelbaum R., Faraggi D. and Ben Arie Y.Survival of diffuse large cell lymphoma. A multivariate analysis including dose intensity variable. *Cancer.* 1990; **66:** 1124-1129.
7. Samolino, E., Chiara R., Montalbetti L., *et al.* Dose-dense R-CHOP-14 supported by peg filgastrim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. *Haematologica.* 2006; **91:** 496-502.
8. Cleaver S. A. and Goldman J. M. Use of G-CSF to mobilize PBSC in normal healthy donors-an international survey. *Bone marrow Transplant.* 1998; **21 (suppl 3):**529
9. Ozer H., Armitag J .O., Bennet C.L., *et al.* Update of recommendations for the use of haematopoietic colony stimulating factors: evidence based, clinical practice guidelines. *J. Clin. Oncol.* 2000; **18:** 3558 - 3585.
10. Crawford J. Risk assessment and guidelines for first-cycle colony-stimulating factor use in the management of chemotherapy-induced neutropenia. *Oncology.* 2006; **20 (5 suppl 4):** 22-28.
11. Frampton J.E., Lee C.R. and Faulds D. Filgastrim. A review of its pharmacological properties and therapeutic efficacy in neutropenia. *Drugs.* 1994; **48:** 731-760.
12. Crowther D., Scarffe J. H., Howell A. *et al.* Growth factor-assisted chemotherapy. The Manchester experience. *Ciba Found Symp.* 1990; **148:**201-214.

13. Pettengell R., Gurney G., Radford J., *et al.* Granulocyte colony stimulating factor to prevent dose limiting Neutropenia in non-Hodgkin's lymphoma: a randomised controlled trial. *Blood.* 1992; **14**:30-36.
14. Schemer R., Geissler K., Kyrle P. A., *et al.* Granulocyte colony-stimulating factor as an adjunct to induction chemotherapy adult acute lymphoblastic leukaemia. *Ann Hematol.* 1993; **66**:283.
15. Ohuo R., Tomonaga M., Kobayadu T., *et al.* Effect of granulocyte colon-stimulating factor after intensive induction therapy in relapsed or refractory acute leukaemia. *N. Engl. J. Med.* 1990; **323**:871.
16. Ohue R., Hiraoka A., Tonimoto M., *et al.* No increase of leukaemia relapse in newly diagnosed patients with acute myeloid leukaemia who received granulocyte colony stimulaitng factor for life-threatening infection during remission induction and consolidation therapy. *Blood.* 1993; **81**:561.
17. Welte K., Reiter A., Menpel K., *et al.* A randomised phase III study of the efficacy of granulocyte colony-stimulating factor in children with high risk acute lymphoblastic leukaemia. *Blood.* 1996; **87** : 3143-3150.
18. Mitchell P. L. R., Morland B., Stevens M. C. G., *et al.* Granulocyte colony stimulating factor in established febrile neutropenia: a randomized study of paediatric patients. *J. Clin. Oncol.* 1997; **15**: 1163-1170.
19. Furman W. N., Fairdongh D. H., Huhu R. D. *et al.* Therapeutic effects and pharmacokinetics of recombinant human granulocyte macrophage colony-stimulating factor in childhood cancer patients receiving myelosuppressive chemotherapy. *J. Clin. Oncol.* 1991; **9**:1022-1028.
20. Macharia W. M. Childhood cancers in a referral hospital in Kenya: A review. *East Afr. Med. J.* 1996; **73**: 647 - 650.
21. Riikoven P., Rahiala J., Salonvara M., *et al.* Prophylactic administration of granulocyte colony-stimulating factor (filgastrim) after conventional chemotherapy in children with cancer. *Stem cells.* 1995; **13**: 289-294.
22. Rusthoven J., Bramwell V., Stephenson B., *et al.* Use of granulocyte colony stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer. *Cancer Prevention and Control.* 1998; **2**:179-190.
23. Heil G., Hoelezer D., Sanz M. A., *et al.* A randomized, double-blinded, placebo- controlled, phase II study of filgastrim in remission induction and consolidation therapy for adults with de novo acute myeloid leukaemia. *Blood.* 1997; **90**: 4710-4718.
24. Radar M. Granulocyte colony-stimulating factor use in patients with chemotherapy induced neutropenia: clinical and economic benefits. *Oncology.* 2006; **20 (5 supp 14)**: 16-21.
25. Tsuge I., Suzuki K., Moriba K, *et al.* Chemotherapy and granulocyte colony stimulating factor for non Hodgkin's lymphoma of the head and neck. *Acta. Otolarygol.* 1996; **525 suppl**: 129-134.
26. Calderwood S., Romeyer F., Blancette V, *et al.* Concurrent Rh GM-CSF does not offset myelosuppression from intensive chemotherapy: randomised placebo-controlled study in childhood acute lymphoblastic leukaemia. *Am. J. Hematol.* 1994; **47**: 27-32.
27. Burdech S. F., Muschenich M., Joseph E., *et al.* Granulocyte-macrophage colony stimulating factor for prevention of neutropenia and infections in children and adolescents with solid tumors. Results of a prospective randomised study. *Cancer.* 1995; **716**:510-516.
28. Dibenedetto S. P., Ragus R., Ippolito A. M., *et al.* Assessment of the value of treatment with granulocyte colony-stimulating factor in children with acute lymphoblastic leukaemia: a randomized clinical trial. *Env. J. Haematol.* 1995; **55**:93-96.