SINGLE DOSE FILGASTRIM IN CYTOTOXIC-INDUCED NEUTROPAENIA IN CHILDREN
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F. K. ABDALLAH

ABSTRACT

Objective: To document the impact of fixed dose weight adjusted filgastrim (G-CSF) in cytotoxic-induced neutropenia.
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 neutropenia.
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 neutropenia; 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 neutropenia 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 × 10⁹/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 neutropenia 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 neutropenia 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 leucopenia. This is because colony stimulating factors (G-CSF and GM-CSF) which are glycoproteins, act on haematopoietic cells to stimulate proliferation, differentiation 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 activity, 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 neutropenia 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 neutropenia 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 neutropenia 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/mm³, a fall in haemoglobin or ANC during the first cycle of chemotherapy (9,10).

Complications of neutropenia 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 hospitalization 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 neutropenia, but even to reduce the incidence of febrile neutropenia (FN) by 50% and concomitant decrease of 35% of hospitalization 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 pediatrics (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 filgastrin 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 filgastrin (G-CSF) in cytotoxic-induced neutropaenic patient. At the POU neutropaenic patients were to receive neuopogen (filgastrin) whenever the neutrophil count fell below 0.5x 10⁹/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 filgastrin 5µg/kg subcutaneously, absolute neutrophil counts before and daily for five days after the filgastrin 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 neutropenia 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 filgastrin 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 filgastrin, 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 0.307 x 10^9/L. Two days (48 hours) after the single dose of filgastrin, 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 x10^9/L with a mean of 5.68 x10^9/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

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Frequency</th>
<th>Gender</th>
<th>Age range</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>11 37</td>
<td>2 9</td>
<td>2-11</td>
<td>VAC-Cis</td>
</tr>
<tr>
<td>ALL</td>
<td>8 27</td>
<td>6 2</td>
<td>9-11</td>
<td>VAP/VAC</td>
</tr>
<tr>
<td>Burkitt’s</td>
<td>9 30</td>
<td>4 5</td>
<td>5-9</td>
<td>CHOP</td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>2 6</td>
<td>1 1</td>
<td>10-12</td>
<td>CHOPP</td>
</tr>
</tbody>
</table>

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

### Table 2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Gender Absolute neutrophil x 10^9/L (nadir neutropenia)</th>
<th>Absolute neutrophil increment count x 10^9/L</th>
<th>Average neutrophil increment %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M F</td>
<td>Mean Range</td>
<td>Mean Range</td>
</tr>
<tr>
<td>VAC-Cis</td>
<td>0 8</td>
<td>0.364 0.18-0.49</td>
<td>4.257 1.302-7.520</td>
</tr>
<tr>
<td>CHOP</td>
<td>5 5</td>
<td>0.284 0.12-0.5</td>
<td>8.016 0.497-26.322</td>
</tr>
<tr>
<td>VAP</td>
<td>3 1</td>
<td>0.249 0.12-0.4</td>
<td>3.482 1.098-6.144</td>
</tr>
<tr>
<td>CHOP +</td>
<td>1 1</td>
<td>0.368 0.28-0.45</td>
<td>9.230 8.284-10.235</td>
</tr>
<tr>
<td>Procarbazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAC</td>
<td>2 1</td>
<td>0.268 0.07-0.45</td>
<td>3.367 0.961-5.184</td>
</tr>
</tbody>
</table>

V = Vincristine, A = 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 Burkitt’s 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).

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 neutropenia 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 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 neutropenia were rhabdomyosarcoma, Burkitt’s lymphoma and ALL. These would subsequently reflect the type of cytotoxic drug schedule used and associated with neutropenia 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 rhabdomyosarcoma (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 acinomyacin 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 ≥2x10⁹/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 filgastrin 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 filgastrin, in the majority of cases (28).

In conclusion this study has shown that a single dose of filgastrin (G-GSF) alleviated chemotherapy induced neutropaenia in most paediatric oncology patients. The absolute neutropaenia 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 neutropaenia (14,17-19). Since a single dose filgastrin 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 filgastrin should first be tried in the management of cytotoxic-induced neutropaenia.

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REFERENCES


