RESEARCH COMMUNICATION

Filgrastim and Antibiotics Treatment Reduces Neutropenia Severity in Solid Cancer Patients

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Abstract

Introduction: Neutropenia has a detrimental effect on cancer patients' quality of life, also possibly resulting in a reduction in the chemotherapy dose which could lead to an increment in the size of a cancer. The main danger associated with neutropenia is the risk of bacterial, fungal or viral infection which may lead to patient death. Treatment including granulocyte-colony stimulating factors (G-CSF, filgrastim) so as to increase the body immunity is given to neutropenic patients with no infection i.e., absence of fever. However, when infection is present, antibiotics such as ceftazidime, imipenem and vancomycin need to be used. Objective: The aim of this study was to find the association between neutropenia severity and treatment with filgrastim (Neupogen®) alone or in combination with antibiotics in solid cancer patients. Methods: This is an observational retrospective study on 117 cases suffering from neutropenia after chemotherapy administration. The patients were admitted to a government hospital for cancer treatment between the years 2003-2006. The types of data collected were categorical and not normally distributed, covering demography, chemotherapy, severity of neutropenia (classified on absolute neutrophil count into mild, moderate and severe) and treatment of neutropenia, either filgrastim (Neupogen®) alone or in combination with antibiotics. Statistical tests used were the Chi-square test, Fisher's exact test and logistic regression. Results: The majority (69.2%) of the patients were treated with filgrastim (81) alone, only 30.8% receiving the combination. Significant associations between both treatments and neutropenia severity. Both Chi-square and Fisher's exact tests showed P= 0.00. Logistic regression showed that filgrastim is the major treatment for severe neutropenic patients since the result showed an infinity (E) and P= 0.00 for filgrastim alone more than its combination with antibiotic. Conclusion: The use of filgrastim is highly associated with treatment of severe neutropenia in solid cancer patients who received chemotherapy. So filgrastim is considered as the drug of choice in the presence of severe neutropenic case.

Key Words: Filgrastim - antibiotics - combination chemotherapy - neutropenia severity

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Introduction

The detrimental effect of neutropenia is the decrease in the quality of life for cancer patients. In addition neutropenia could also result in the reduction of chemotherapy dose which could lead to an unwanted increase in the size of the cancer. When neutropenia occur in cancer patients due to chemotherapy it will lead to an 85% reduction of the required doses of the chemotherapy used (Gabrilove, 2006; Lyman and Wilmot, 2006). So this study looked at the treatment which will help to overcome problems associated with the neutropenic patients lives. Fortner and his colleagues (2005) showed that neutropenia has a negative effect on chemotherapy use in cancer patients since these chemotherapeutics drugs will also kill other rapidly growing cells such as bone marrow cells and blood cells apart from the cancer cells. Dale (2005) showed that this serious side effect of the chemotherapy is due to anti-metabolic effects on folic acid production which will result in prevention of cell production especially neutrophils. This anti-metabolic effect blocks DNA, RNA and protein synthesis which will lead to bone marrow depletion, and thus a decrease in neutrophil cell production (Verstraete et al., 1997; Frey, 1999; Linker, 2000; Frey and Granger, 2002).

The main danger associated with neutropenia is bacterial, fungal and viral infection, which may lead to serious problems and death (Linker, 2000; Greene, 2004). Zia Rahman and her colleagues (1997) documented a dangerous association between neutropenia, fever and infection on cancer patients . Hence there have been many studies focusing on treatment of neutropenia to overcome these problems. The drugs used include granulocyte-colony stimulating factor (G-CSF, filgrastim) (Neupogen®) which increases the body immunity by increasing neutrophil cell production. This is usually given when there is no infection i.e. absence of fever. But when infection is present antibiotics like ceftazidime, imipenem

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and vancomycin will be used (Frey and Granger, 2002).

Great results were obtained in a study by Timmer-Bonte et al, when combination of GCS-F and antibiotics solved the neutropenia problem in cancer patients who were on chemotherapy (Timmer-Bonte et al., 2005). G-CSF is very effective for solid cancer patients treated with chemotherapy and suffered from different levels of neutropenia (Gabrilove, 2006). These results were also stated in the guidelines of both National Comprehensive Cancer Network (NCCN®) and the American Society of Clinical Oncology (ASCO). While antibiotics treatment either single or combination has also been shown to be important in overcoming infection especially bacterial infection in neutropenic patient. Bacterial infection especially those caused by either *Pseudomonas aeruginosa* or *Acinetobacter baumannii* needed combination antibiotics specifically beta-lactam and aminoglycoside which is very important and effective, since these types of bacteria are usually antibiotics resistance (Ohyashiki, 2004; Rahal, 2006). However, for treatment of severe neutropenia antibiotic is preferred to be given with filgrastim since the use of antibiotic alone without filgrastim will be harmful rather than being useful. This is because the use of antibiotic alone will lead to increase inbacterial resistance and will not increases the neutrophil cell count (Dale, 2004). Thus filgrastim needs to be added.

Materials and Methods

The approval letter for conducting this study was obtained from the clinical research center (CRC) of the government hospital. This was an observational, retrospective study among solid tumor cancer patients who developed neutropenia due to chemotherapy treatment and was admitted to the hospital between the years 2003-2006. The aim of this study was to find the association between neutropenia severity with the use of filgrastim (Neupogen®), combination of filgrastim and antibiotic as well as with antibiotic alone as the treatment among severe neutropenic cancer patients of the hospital.

The total number of cancer patients files screened was 4,503 and the number of neutropenic patients fulfilling the study criteria was 117. The inclusion criteria were patients diagnosed with solid cancer, adult ≥ 18 years old, both male and female, suffered from neutropenia or febrile neutropenia after receiving chemotherapy, their files available in both the oncology clinic and the record office of the hospital and the patient should be admitted to the oncology ward. The power of this study was more than 87.5%. The data collected were categorical and not normally distributed. They were analysed with the data for neutropenia severity, classified based on the absolute neutrophil count (ANC) which include mild (ANC < 1500-1000 cell/ μl), moderate (ANC < 1000 cell/ μl and > 500 cell/ μl) or severe (ANC ≤ 500 cell/ μl) neutropenia.

Since the objectives of the study were to look for risk factors, thus the non-parametric tests i.e., Chi-square test and Fisher's Exact test were more relevant. Significance was achieved with a P value <0.05. Then logistic regression test for odds ratios and P value <0.05 were performed for variables with significant association. This was to detect the most significant variable that was highly associated with neutropenia severity treatment.

Table 1. Types of Treatment for Neutropenic Patients

Treatment	Number of Patients	Percentage
Filgrastim	81	69.2
Antibiotics and Filgrastim)	36	30.8
Total	117	100.0

Results

Types of treatment given to neutropenic patients are as listed in Table 1. Majority of the neutropenic patients were treated with filgrastim (Neupogen®) alone (n= 81; 69.2%) and followed with combination of both filgrastim and antibiotic (n= 36; 30.8%). Obviously none of the neutropenic patients were treated with antibiotics alone. The P values obtained from using both Chi-square and Fisher's Exact tests were 0.00 respectively. Thus this indicated that there was a significant association between these drugs treatment with neutropenia severity. The Logistic Regression test was used to determine which of these three variables were highly associated with neutropenia severity. The Odd Ratio and P value showed that filgrastim is the most highly associated with neutropenia severity treatment since the value for it was E (infinity) and P= 0.00.

Discussion

In this observational retrospective study it was observed that neutropenic patients were treated with antibiotics and / or filgrastim (Neupogen®) as shown in Table 1 and none of the patients were treated with antibiotics alone. A large proportion of the patients that is 69.2% were treated with filgrastim while 30.8% of the neutropenic patients were treated with both antibiotics and filgrastim. After using the Statistical Package for Social Sciences (SPSS®) version 15, the results showed that there was a significant association between the treatment options with neutropenia severity since the P- value of Chi-square test= 0.00 and the Fisher's Exact test= 0.00. The Logistic Regression test showed an Odd Ratio= E (Infinity) with P- value = 0.00 for the treatment with filgrastim. This means that filgrastim treatment is strongly associated with neutropenia severity. So when the severity of neutropenia increased the used of the filgrastim also increased. In this study patients having neutropenia without fever were treated with only filgrastim, while those patients with febrile neutropenia were treated with both antibiotics and filgrastim, however antibiotics alone was not used in either condition.

The reason for using only filgrastim is to stimulate production of neutrophil cells hence increasing the patient's immunity. The absence of fever among this group of neutropenic patients indicates that there is no infection thus antibiotic treatment is not needed. However in febrile neutropenia where infection is present using only filgrastim will only lead to increase in the neutrophil count

but would not treat the infection. While if only antibiotic was used this will only treat the infection but the risk of infection will remain the same since neutrophil count would still remain low. Thus both treatments are important for the management of febrile neutropenic patients (Dale, 2004). Also the use of the antibiotic alone will lead to an increase in the occurrence of bacterial resistance. Therefore to ensure successful treatment, filgrastim which is the most important treatment must be added to the antibiotic. Thus this explains the strong association seen between filgrastim treatment and neutropenia severity (Dale, 2004). There is also suggestion that colony stimulating factors such as filgrastim could be given to cancer patients on chemotherapy even if there is no neutropenia. This is to ensure that the WBC (i.e., neutrophil cell) is maintained within the normal level and the body is protected from any type of infection (Dale, 2005).

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