RESEARCH COMMUNICATION

Association of Neutropenia Onset and Severity with Chemotherapy Regimens and Schedules

Bassam Abdul Rasool Hassan*, Zuraidah Binti Mohd Yusoff, Saad Bin Othman

Abstract

Introduction: Neutropenia, defined as a decrease in the absolute neutrophil count lower than the normal that is < 1500 cell/ µl, 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. There are so many causative factors for neutropenia like hematological disorders, autoimmune diseases and infection, drugs reactions and chemotherapy or radiotherapy. So the main aim of this study is to find the association between chemotherapy drug or regimens, schedule of administration used for treatment of solid cancer diseases with neutropenia onset and severity. Methods: This is an observational retrospective study carried out in a general hospital on 117 solid tumor patients who admitted between January 2003 to December 2006. The main statistical tests used were Chi-square test and Fisher's Exact test. The significance of the result will be when the P < 0.05, while the confidence interval for this study was 95%. Results: The highest chemotherapeutic regimen was (5-FU + epirubicin + cyclophosphamide) (47, 40.2%) followed by (gemcitabine + cisplatin) (6, 5.1%) and many others. Majority of the patients receive their chemotherapy schedule of administration was one day schedule (90, 76.9%) followed by more than one day schedule (27, 23.1%). Conclusion: The doses of these drugs were not high enough to produce a sufficient pharmacological effect to cause bone marrow suppression and lead to neutropenia. Besides the schedule of administration for each drug was long enough to overcome neutropenia also the high uses of granulocyte colony stimulation factor (G-CSF) which will play a major role in reducing the time and severity of neutropenia. All these factors play an important role in giving non- significant association between neutropenia onset and severity with chemotherapeutics drugs and their schedule of administration.

Keywords: Chemotherapy drugs - schedule of administration - - neutropenia - onset - severity

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Introduction

There are so many causative factors for neutropenia like hematological disorders, autoimmune diseases and infection, drugs reactions and chemotherapy or radiotherapy (Dale, 2005). Solid tumor patients usually characterized by normal function and level of neutrophil cell could developed neutropenia as a result of chemotherapeutics drug and regimens (Rolston, 2001). The chemotherapeutics drugs caused bone marrow destruction mainly by their anti metabolic effect which will lead to prevention of the DNA & RNA synthesis this will lead to bone marrow suppression and destruction (Dale, 2005; Frey, 1999; Frey, 2002; Linker, 2000; Verstraete et al., 1997). This bone marrow destruction will lead to a decrease in the neutrophil cell production and as a result neutropenia developed as one of the major chemotherapy side effect. The patient is started to be considered as neutropenic when the absolute neutrophil count is lower than the normal level which is 1500 cell/ μl. The chemotherapy anticancer effect is due to the suppression on any highly active dividing cells mainly cancer cells, but as a result from that normal blood cells and bone marrow will effected also (Fortner et al., 2005). Examples of chemotherapeutic drugs which are highly associated with neutropenia are Actinomycin, Asparaginase, Busulfan, Cisplatin, Doxorubicin, Daunorubicin, Etoposide, Fluorouracil, Ifosfamide and Methotrexate (Dale, 2005; Linker, 2005; Kimble-Koda et al., 2002). Chemotherapy treatment is preferred to be given in a continues basis in order to get its maximum therapeutic benefit of cancer cell killing and to decrease the development of cancer cell resistance. The time of receiving chemotherapy is considered as the course of the chemotherapy or cycle and between each cycle there is an interval period of 21-28 days which is very important for recovery of the normal cells from chemotherapeutics toxic effect (Scurr et al., 2005). The duration of each administration is determined by the pharmacokinetics and pharmacodynamic of each chemotherapeutics drug. Some of these drugs when given in one day will produce the desired anticancer effect with low side effects, while others because of their severe side

*Clinical Pharmacy Discipline, School of Pharmaceutical Sciences, University of Sains Malaysia, Minden, Penang, Malaysia *For correspondence: bassamsunny@yahoo.com*

effects must be given over a longer duration of more than one day in order to produce the anticancer effect with the prevention or reduction of their side effect (Scurr et al., 2005). An example of this is 5-flourouracil which when administered over a longer duration will lead to inhibition of DNA and RNA synthesis of the cancer cells, while when given as a single and bolus dose will lead to inhibition of thymidylate synthesis that caused bone destruction and severe neutropenia. While paclitaxel has the opposite result that is when given over long duration that is more than one day will lead to increase in more destruction of the bone marrow (severe neutropenia), while when given in one day will result in desired anticancer effect (Scurr et al., 2005).

Materials and Methods

Study design and setting

This is an observational retrospective study was conducted on solid cancer patients treated in this hospital. Ethical approval letter for conducting this study was obtained and granted from the clinical research center (CRC) of the hospital which is identical and follow to the declaration of Helsinki 1964. This study covered retrospectively the period between the period 1 January 2003 and 31 December 2006. A total of 117 patients fulfilling the inclusion criteria were selected from the total number of 4503 solid cancer patients. All of 117 patients suffered from neutropenia cancer after chemotherapy treatment. All of them were identical to the inclusion criteria of the study. The main aim of this study is to find the association between chemotherapeutics regimen and their schedules with onset and severity of neutropenia i.e., its main risk factors for its incidence and severity.

Inclusion and exclusion criteria

The inclusion criteria for this study were the patients must suffer from solid cancer, male or female adult ≥ 18 years old, treated with chemotherapy, their files must be found in the oncology clinic and record office of the hospital and must be admitted to ward C19. While the exclusion criteria were all the pediatric patients will excluded, all the patients who suffer from neutropenia as a result from hematological diseases not caused by chemotherapy, all the patients who treated with radiotherapy and as a result of that they suffer from neutropenia and all the patients who did not admitted to ward C19.

Data collection

All the data collected were retrospectively from the patients files which were found in the oncology clinic and the record office of the hospital. These data were collected by the uses of a special data form sheet which was already design for this study. So all the patients who admitted to the hospital between 1 January 2003 and 31 December 2006 files were retrospectively reviewed. After that all the clinical information obtained were keyed into SPSS® software program, which by it all the statistical analysis to find if there is an association between neutropenia onset and severity on one side and with types of chemotherapeutics drugs or regimens and their schedule of administration on the other side.

Table 1. Chemotherapeutic Drugs or Regimens Used (n=117)

Chemotherapeutics Drugs or Regimens	Freq	%
1 5-FU + Epirubicin + cyclophosphamide	47	40.2
2 Gemcitabine + cisplatin	6	5.1
3 Cisplatin + 5- FU + F.A	6	5.1
4 Paclitaxel + cisplatin	4	3.4
5 5-FU + F.A	3	2.6
6 5-FU + methotrexate + cyclophosphamide	3	2.6
7 Doxorubicin + cyclophosphamide	3	2.6
8 Paclitaxel + cisplatin + pamisol	3	2.6
9 Paclitaxel + cyclophosphamide + epirubicin	3	2.6
10 Temozolomide + vincristine	3	2.6
11 Gemcitabine + ifosfamide + 5-FU +folinic acid	2	1.7
12 Paclitaxel + epirubicin	2	1.7
13 Gemcitabine	2	1.7
14 Gemcitabine+ carboplatin+ cisplatin+ paclitaxel	2	1.7
15 Capecitabine	2	1.7
16 Cisplatin + vinorelbine	2	1.7
17 Vinblastine	2	1.7
18 Doxorubicin + cisplatin	2	1.7
19 Docetaxel + cisplatin	2	1.7
20 Cisplatin + docetaxel	2	1.7
21 Vinorelbine + 5-FU + folinic acid	2	1.7
22 Cyclophosphamide + epirubicin + vincristine	1	0.9
23 6-mercaptopurine + Ara-c	1	0.9
24 Irinotecan + 5-FU + folinic acid	1	0.9
25 Gemcitabine + carboplatin	1	0.9
26 Vinorelbine	1	0.9
27 Vinorelbine + etoposide + bleomycin	1	0.9
28 5-FU + cisplatin	1	0.9
29 Gemcitabine + vinorelbine	1	0.9
30 5- FU + vinorelbine	1	0.9
31 Capecitabine + 5-FU + folinic acid	1	0.9
32 Paclitaxel + cisplatin	1	0.9
33 5-FU + 5-FU	1	0.9
34 Paclitaxel+ cisplatin+ gemcitabine+ ifosfamide	1	0.9
35 Vincristine	1	0.9
36 Cisplatin + bleomycin + etoposide	1	0.9
37 Paclitaxel + cisplatin + ifosfamide	1	0.9

5-FU, 5-Fluorouracil; Ara-c, Cytosine arabinoside = Cytarabine.

Statistical analysis

The power of this study according to its sample size was more than 87.5% i.e., since the power of the study > 80 then the results of this study can be dependable. The type of the data collected were a categorical data which included 37th of different chemotherapeutics regimen used for treatment of different solid cancer diseases. While about information related with schedule of administration the data were also categorical which included whether the patient receive their chemotherapy within one day schedule or within more than one day schedule. On the other side it include neutropenia onset depend on the time when its start after chemotherapy administration and its classified as the following within the first week after receiving chemotherapy ≤ 7 days, within two weeks after chemotherapy administration 8-13 days and more than or after two weeks ≥ 14 days) and neutropenia severity which classified according to absolute neutrophil count (ANC) which include (Mild when ANC < 1500 cell/ μL and >

1000 cell/ μL, Moderate when ANC < 1000 cell/ μL and > 500 cell/ μL, Severe when ANC ≤ 500 cell/ μL). These data are not normally distributed this has been confirm after the uses of the SPSS® program since the (P= 0.003, Kolmogoonov-Smirnov test). Since the main objective for this observational study is the looking for association and risk factors and since the data was categorical then the main statistical test which is suitable is Chi-square test and significance was set at P value < 0.05. The confidence interval for this test is 95%. The data were analyzed by using SPSS® version 15 program to see the association between these chemotherapeutics and neutropenia onset and severity.

Results

Chemotherapeutics regimens

The result in Table 1 showed that neutropenia among the 117 solid cancer patients studied were caused by many types of chemotherapeutics regimens. The main chemotherapy regimen causing neutropenia was 5-FU + cyclophosphamide + epirubicin (42, 40.2%) which is mostly used for the treatment of breast cancer. While the rest of the 59.8% of neutropenic cases were caused by the other 36 chemotherapeutics regimens which were used for treatment of nasopharyngeal cancer, rectum cancer, brain cancer, lung cancer and many others types of solid cancer diseases. The majority of the patients (76.9%, n= 90) were treated with one day chemotherapy while 23.1% (27) were treated with more than one day schedule of chemotherapy regimen.

Statistical analysis

However the statistical analysis of Chi-square test results showed insignificant associations between chemotherapy types and neutropenia onset with P value of 0.798 (P> 0.05) and neutropenia severity (P value = 0.199). The result of the statistical analysed by Chi-square for neutropenia onset (P value = 0.689) and severity P value of 0.434. Fisher's Exact tests result with neutropenia onset with P value = 0.206 and for severity (P value = 0.304) with chemotherapy schedule or duration. So the results showed there were insignificant associations between the chemotherapy duration with both the neutropenia onset and severity since the P values for both were > 0.05. The confidence interval for these statistical tests that used for detecting the association with onset and severity of neutropenia were 95%.

Discussion

The results of this study showed that there were many types of chemotherapeutic regimens used for treatment of solid cancer that resulted in neutropenia as shown in the Table 1. However, there were no significant associations between these chemotherapeutics regimen and neutropenia onset or severity. Chemotherapeutics drugs and regimens are considered as one of the main cause for neutropenia occurrence in cancer patients as been reported by many references (Demirkan et al., 2006; Buffoni et al., 2006; Kern, 2001). However significance was not achieved in this study. This might be due to the intensity of the chemotherapeutics drugs used. Most probably the dose of these chemotherapeutics drugs used in this presented study was not very high (i.e., not intensive enough) to cause myelosuppression so to cause or produce neutropenia. So this could be most probable reason for the insignificance association with neutropenia onset and severity (Kern, 2001). This conclusion mentioned by Nakata et al that there is chemotherapeutics drugs dose not produce side effect (i.e., neutropenia), this is because either these drugs not used in their recommended dose or not administered in sufficient doses (Nakata et al., 2006).

A very important explanation for this insignificant association observed could be because of the use of G-CSF (Filgrastim ®) that leads to stimulation of the bone marrow to produce mature neutrophil cells. In addition the chemotherapy administration interval period between each cycle (21-28) days is long enough for bone morrow recovery and production of mature neutrophil cells thus overcoming neutropenia (Rugo, 2000). Another explanation which is the small sample size in comparison to the numbers of chemotherapeutics drug or regimens used in this study was small. Even though there are studies with small sample size reporting significant association between neutropenia and chemotherapy because the numbers of the chemotherapeutics drugs involved were only one or two. Example Demirkan et al studied only on only 60 patients but the numbers of chemotherapeutics regimens involved was only 2 thus resulting in a significant association (Demirkan et al., 2006). Another study by Buffoni et al here also showed significant association among 30 patients enrolled but only 2 chemotherapeutics drugs were used (Buffoni et al., 2006). So all these could explain the insignificant association that obtained in this presented study.

While for the schedule of chemotherapy use or administration is dependent on its type and intensity because of the severe bone marrow suppression such as with the alkylating agent e.g. cyclophosphamide. These types of chemotherapeutics more preferable to be used by using pulse method which mean that the chemotherapeutics are administered for short period and subsequent doses or cycles are given after a long interval so as to a give sufficient time for bone marrow and neutropenia to recover (Rugo, 2000). Thus in this study the explanation for the insignificant association between onset and severity of neutropenia with chemotherapy schedule is because these chemotherapeutics drugs were used following the pulse method. The drugs were given for a very short period that is for one to 3 days and subsequent second cycle was given after a long period of 21-28 days which is enough for the recovery of neutropenia (Rugo, 2000). Also the use of G-CSF (filgrastim) play a major and important role in increasing the rate and reducing the time for the bone marrow to recover and produce mature neutrophil cells (Scurr et al., 2005). The result of this present study was oppose the result found by Nitta et al. (2006) who reported that there was an association between the chemotherapy duration and onset of neutropenia (Nitta et al., 2007). Also Hainsworth et al. (2005) found that there was a

significant association between chemotherapy schedule and neutropenia. The main cause for their significant association is the high intensity of the chemotherapeutics drugs used which were carmustine, cyclophosphamide, methotrexate, 5-flourouracil and prednisone (Hainsworth et al., 2005).

So this study concluded that the sufficient dose of the chemotherapeutics drugs and their intensity are the main causes for neutropenia incidence or severity so when the doses or intensity were low this will lead to insignificant association, or because of the interval period between doses was long enough to overcome neutropenia. Also the uses of the G-CSF help to reduce both the duration for bone marrow recovery and reduce the severity of neutropenia. Both of the long interval and uses of G-CSF are both consider as the major reasons for the insignificant association between chemotherapy schedule and neutropenia onset and severity.

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