RESEARCH COMMUNICATION

Association and Correlation of Different Chemotherapeutic Regimens and Doses With Onset and Severity of Anemia Among Solid Cancer Patients

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Abstract

Introduction: Anemia is considered as one of the most frequent hematological demonstration of malignant diseases, which lead to momentous impairment in every tissues and organs of cancer patients and put them under serious stress. This major problem may arise because of the underlining diseases (i.e., cancer diseases) or radiotherapy or chemotherapy treatment received. This present study tries to find the association between anemia onset and severity with different chemotherapeutics regimens used in the treatment of several solid cancers and to find the association of anemia onset and severity with different doses of these chemotherapeutics drugs. Methods: This retrospective observational study was conducted in Penang General Hospital on 534 anemic solid cancer patients who were admitted between 2003 and 2009. The main statistical tests used were Chi-square test and Logistic regression test for categorical data. While for continues data the main statistical tests were Linear regression and correlation test. The significance of the result will be when the P < 0.05, while the confidence interval for this study was 95%. Results: FEC, 5-FU+5-FU, Docetaxel and Cisplatin+ 5-FU regimen has strong association and correlation with anemia onset and severity. However the associations and correlations with anemia severity were stronger than those with the onset. Different doses of 5-FU, cyclophosphamide, docetaxel and cisplatin play a critical role in anemia onset and severity. Conclusion: Monitoring and determination of hemoglobin levels for cancer patients treated with FEC, 5-FU+5-FU, Docetaxel, Cisplatin+ 5-FU specifically with high doses must be emphasized and a focus of particular attention.

Keywords: Anemia - chemotherapy regimens - doses - solid cancers

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Introduction

Anemia is a condition characterized by lack of blood or in other word a reduction of total quantity of erythrocyte (red blood cells, RBC) or hemoglobin in the circulation which are necessary for normal function. This is caused by the inability of the bone marrow to replace the erythrocyte lost. The normal level of RBC for the male is 5.4×106 cell/ μl and for female is 4.8×106 cell/ μl (Haut, 2007; Blaser, 2001; Haggerty, 1999; Brown and Olde, 2005). Anemia is one of the common side effect of chemotherapy especially with the myelosuppressive type. Incidence and severity of the anemia mainly depend on different factors which are the type of chemotherapy, chemotherapy schedule, chemotherapy intensity as well as the type of cancer. Single or combination chemotherapy play a serious and major role in anemia incidence and severity since the use of combination chemotherapy regimen lead to severe anemia more than the use of single chemotherapy drug (Groopman and Itri, 1999; Barett-Lee et al., 2006; Ruggiero et al., 2008). Besides the myelosuppressive effect of chemotherapy, anemia can also happen due to the direct destruction of the RBC it self (i.e., direct effect on the erythropoiesis in the bone marrow) or due to reduced erythropoietin production (i.e., impact on EPO production). When this chemotherapy drugs are used repetitively this may lead to prolong production of anemia. Also the results obtained from clinical trials showed that the probability of mild anemia incidence after the use of chemotherapy is 100%, while the probability of severe anemia incidence after chemotherapy is 80%. From these results and data it has been proven that chemotherapy is the major impact factor for anemia onset and severity in cancer patients (Glaspy et al., 2001; Cazzola, 2000; Danova et al., 2000; Groopman and Itri, 1999; Beguin, 2005). Anemia caused a broad spectrum of negative symptoms which may vary from negligible to life threatening condition. Fatigue is one of the major side effects of anemia that is significantly associated with physical, emotional, psychological and emotional consequences. According

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to the survey conducted by Vogelzang and his colleague, 61% of the 400 cancer patients studied mentioned that fatigue has an impact virtually on their lives more than cancer related pain (Vogelzang, et al., 1997; Pohl and Ludwig, 2005). Besides that, anemia is also associated with tumor hypoxia which could induce more malignant tumor phenotype and more angiogenesis. These sequels will lead to significant reduction in efficacy of cancer treatment. Kirshner and his colleague mentioned that there is only little information related with the association of anemia incidence and severity with several adjuvant chemotherapies used for treatment of various stages of breast cancer disease (Krishner et al., 2004). Also Goldrick et al, (2007) mentioned that the incidence and severity of anemia with different modern chemotherapy regimens used for the treatment of early stages of breast cancer is still unclear and not documented. Thus this present study is not only looking at early stages of breast cancer but will look at most of the solid cancer diseases thus would be the first study to help in clarifying these points. Besides that this study also tries to find the association of anemia with these chemotherapy regimens doses and determine which are the most highly associated regimen and/ or dose of these chemotherapeutics drugs with anemia onset and/ or severity.

Materials and Methods

Study design and setting

This is a retrospective observational study, conducted in a government hospital on Penang island i.e., Penang General Hospital which is the biggest public hospital in Penang. Penang island is located in the northwest of Malaysia and is separated from the west-coast of Malaysia by five kilometer channel. The approval letter for this study was issued by one of the research institute under the National Institutes of Health (NIH). These are the Institute for Medical Research (IMR), Clinical Research Centre (CRC), Institute of Public Health (IPH), Institute for Health Management (IHM), Institute for Health Systems Research (IHSR), and Institute for Health Behavioral Research (IHBR). Approval was also issued by Ministry of Health Malaysia (MOH). All mentioned above are with the declaration of Helsinki 1995 (as revised in Tokyo in 2004).

Patients

This study was conducted among cancer patients admitted to Penang Hospital who suffered from solid cancer and were treated with chemotherapy. As a result of the presence of solid cancer and/ or the use of chemotherapy, these patients suffered from anemia.

Data collection

This was carried out by reviewing all the patients files found in the oncology clinic of Penang Hospital from 2003 to 2009. From this review adult solid cancer patients age ≥ 18 years old admitted to and treated with only chemotherapy and have a record of anemia were chosen. Any patients suffering from hematological cancer type or treated with radiotherapy or have an inherited problem with Hb or pancreas problems were excluded.

The variables collected in this part of the study include data on patient demography, solid cancer types and stages, anemia onset and severity after receiving chemotherapy, types of chemotherapy regimens used for treatment of solid cancers and chemotherapeutics drugs doses received by the anemic patients.

There are two types of data collected which are categorical data which represent the types of chemotherapy regimens received by patients and onset and severity of anemia after receiving the chemotherapy. While the other type of data was continuous data which represent the doses of chemotherapeutics treatments received by those patients. For the categorical data were non-normally distributed and was confirmed by the Statistical Package of Social Sciences (SPSS®) software program version 15 thus non parametric test were used to analyze them. The data were entered into the SPSS® software program version 15, for analysis. The type of statistical test used was Chi-square because as mentioned above. In addition, this study was an observational study looking for association and hence this test is applicable. This test mainly depends on the frequency of the variables, since Chi-square required frequency for each cell to give a dependable result of not less than 5 times. Also data showing frequency lower than 5 times must not be more than 20% of the total data. The results were considered significant when $P < 0.05$ with confidence interval of 95%. The power for this study was more than 95%. For data which show significant results with Chi-square test, Logistic regression test was used to detect the type of chemotherapeutics regimens which are highly associated and correlated with anemia onset and severity. The two main parameters determining the risk factor most associated with these conditions are firstly the P value which must be significant that is < 0.05 and secondly the factor must have the highest Odd Ratio. While for continues data, Pearson correlation test since the data was un normally distributed this confirmed by using Kolmogorov-Smirnov test the result was $P < 0.05$, also this test used to detect the type of correlation between chemotherapeutic drug doses with anemia onset and severity. Whether if it is positive or negative correlation this is depends on (r) value which arrange between (+1 to -1). But the correlation value meaningless if P insignificant i.e., P it must be < 0.05. While for those data which showed significant correlation, Linear regression test was used in order to find the most strongly correlated and associated of chemotherapeutic drugs doses with anemia onset and severity. This will mainly depend on B value which will show the type of correlation whether positive or negative one, β value which will show the strength of correlation between the two variables, and all these values will be meaningless if P value not significant.

Results

Patient characteristics

The majority of the anemic patients (n=534) were women (n=336; 62.9%) while male represent only 37.1% (n=198). Chinese was the predominant race (n=305; 57.1%), followed by Malay (n=178; 33.3%) and finally

Table 1. Prevalence of Anemia among Solid Cancer Patients (n=534)

Anemia variables	Value
Anemia presence (n=534)	
Before chemotherapy	126 (23.6%)
After chemotherapy	
408 (76.4%)	
Onset of anemia after chemotherapy (n=408)	
1st cycle	2 (0.5%)
2nd cycle	75 (18.4%)
3rd cycle	153 (37.5%)
4th and more cycle	178 (43.6%)
Severity of anemia (n=408)	
Mild (Hb= 10.9-10 g/ dL)	124 (30.4%)
Moderate (Hb= 9.9-7 g/ dL)	242 (59.3%)
Severe (Hb ≤ 6.9 g/ dL)	42 (10.3%)

Table 2. Types of Chemotherapy Used in Anemic Patients (n=408)

	Chemotherapeutics Drugs or Regimens	Frequency	%
1	5-FU + epirubicin + cyclophosphamide	108	26.5
2	5-FU + 5-FU or 5-FU	86	21.1
3	Docetaxel	42	10.3
4	Cisplatin + 5- FU	42	10.3
5	FOLFOX	26	6.4
6	Cisplatin	11	2.7
7	Gemcitabine + cisplatin	11	2.7
8	Cisplatin+ 5-FU+ epirubicin	10	2.5
9	Bleomycin+ etoposide+ cisplatin	9	2.2
10	Irinotecan + 5-FU + 5-FU	6	1.5
11	Gemcitabine	6	1.5
12	Cisplatin+ doxorubicin	5	1.2
13	CMF	5	1.2
14	Paclitaxel + cisplatin	4	0.9
15	Taxol+ cisplatin	4	0.9
16	Etoposide+ cisplatin	4	0.9
17	Cisplatin+ docetaxel	3	0.7
18	Capecitabine (Xeloda)	3	0.7
19	Navelbin+ cisplatin	2	0.5
20	Carboplatin	2	0.5
21	Paclitaxel + cisplatin + ifosfamide	2	0.5
22	Vinorelbine	2	0.5
23	Carboplatin+ etoposide	1	0.5
24	FAC	1	0.2
25	Carboplatin+ gemcitabine	1	0.2
26	Epirubicin+ cyclophosphamide	1	0.2
27	Vinirolibin+ 5-FU	1	0.2
28	Cyclophosphamide+ doxorubicin+ cisplatin	1	0.2
29	Cyclophosphamide+ methotrexate+ 5-FU	1	0.2
30	Methotrexate+ vinblastine+ cisplatin	1	0.2
31	Oxaloplatine	1	0.2
32	Doxorubicin+ cyclophosphamide	1	0.2
33	Ifosfamide+ 5-FU	1	0.2
34	Taxol+ carboplatin	1	0.2
35	Carmustin	1	0.2
36	Epirubicin+ cyclophosphamide	1	0.2
37	Almira	1	0.2
	Total	408	100

*5-FU1 Dose= 5-FU first or bolus dose/ 5-FU2= 5-FU the second dose after bolus

the Indian (n=51; 9.6%). Their mean age was 53.3 years (range, 18–93 years). Most of the patients (n=148; 27.7%) were between 60-69 years old. Majority of the anemic patients suffer from breast cancer (n=186; 34.8%), followed by those who suffered from rectum cancer (n=64; 11.9%), then came colon cancer 50 (9.4%). Most of them (n=246; 46.1%) suffer from third stages disease and a small number (n=246; 46.1%) had early-stage disease.

Prevalence of anemia

One hundred and twenty six (126; 23.6%) of the total 534 patients suffered from anemia before receiving chemotherapy, while 408 suffered from anemia after receiving chemotherapy. In this present study, only patients with anemia after receiving chemotherapy will be discussed. For the onset of anemia after receiving chemotherapy, 178 (43.6%) of the 408 patients developed anemia after the 4th and more administration of chemotherapy. Followed by those who showed onset of anemia after 3rd administration of chemotherapy (153; 37.5%), then after 2nd administration (n=75; 18.4%) and finally after 1st administration (n=2; 0.5%). As for severity, majority of the anemic patients suffered from moderate anemia (n=242; 59.3%), followed by mild anemia (n=124; 30.4%) and finally severe anemia (n=42; 10.3%). Severity is dependent on the Hb level. All these data are tabulated in Table 1.

Chemotherapy types and doses

The regimen that seems to be most highly linked to anemia is the combination of 5-Fluorouracil (5-FU), Epirubicin and Cyclophosphamide (108; 26.5%) especially for the treatment of breast cancer. Secondly, the 5-FU + 5-FU or 5-FU regimen (n=86; 21.1%) then docetaxel and cisplatin + 5- FU regimens (n=42; 10.3%). These are shown in Table 2.

Among these cancer patients who developed anemia after chemotherapy, 64 (7.2%) were treated with high doses of ≥ 1000 mg 5-FU1. This is followed by these treated with 900-999 mg of 5-FU1 (n=59; 6.7%), ≥ 100 mg epirubicin ≥ 1000 mg cyclophosphamide each 54 patient (6.1%).

Statistical analysis

According to the statistical tests, there were a significant association between onset and severity of anemia after chemotherapy with type of chemotherapy regimen. The results also showed that the association between onset of anemia with chemotherapy types is weaker than the association between anemia severity with chemotherapy types since Chi-square P values for association with onset is 0.026 while for association with severity it is 0.007. The results of logistic regression showed that the type of chemotherapy highly associated with anemia onset and severity were FEC (P=0.011; odd ratio 2.310), 5-FU plus 5-FU or 5-FU (P=0.03; odd ratio 2.112), Docetaxel (P=0.024; odd ratio 1.978), Cisplatin+5-FU (P=0.041; odd ratio 1.839) and finally others chemotherapies (P= 0.049; odd ratio 1.241).

While with anemia severity, the results show that the chemotherapy types association with anemia severity is greater than its association with anemia onset and that FEC is highly associated with anemia onset and severity (P=0.019; odd ratio 3.223) followed by 5-FU+5-FU or 5-FU (P=0.024; odd ratio 2.448) docetaxel (P=0.035; odd

ratio 2.121), 5-FU + cisplatin (P= 0.037; odd ratio 1.467) and lastly others (P=0.039; odd ratio 1.112).

The Pearson correlation test results show that 5-FU1 (i.e., the bolus dose given as a part of FEC regimen or 5-FU+ 5-FU regimen) dose ≥ 1000 mg has the greatest association and correlation with anemia onset (P= 0.000; r= 0.935), 900-999 mg (P= 0.010; r= 0.774), 800-899 mg (P= 0.041; r= 0.566), 700-799 mg (P= 0.049; r= 0.522) but other doses (600-699 and 400-599) show insignificant association. As for cyclophosphamide, only ≥ 1000 mg dose (P= 0.031; r=0.864) and 900-999 mg dose (P= 0.045; r= 0.713) showed significant association with anemia onset while the rest did not. For epirubicin all of the doses show insignificant association with anemia onset. While for 5-FU2 (the second dose in 5-FU+ 5-FU regimen) i.e., the dose given on the second day after the bolus dose of 5-FU1, only the dose ≥ 700 mg show significant association (P= 0.043; r=0.526). For cisplatin only the dose ≥ 100 mg show significant association with anemia onset (P= 0.047; r=0.731) and for docetaxel only ≥ 110 mg dose show significant association with anemia onset (P= 0.049; r=0.883). As for the other doses in the chemotherapeutic treatments, all show insignificant association with anemia onset.

The Pearson correlation test results for the association of chemotherapy doses with anemia severity, show that 5-FU1 ≥ 1000 mg dose has the strongest association and correlation with anemia severity (P= 0.000; r= 0.962), 900-999 mg dose (P= 0.005; r= 0.832), followed by 800-899 mg dose (P= 0.033; r= 0.797) and finally the 700-799 mg dose (P= 0.047; 0.511). For cyclophosphamide, the doses that showed significant association with anemia severity were ≥ 1000 mg (P=0.02; r=0.922) and 900-999 mg (P= 0.033; r=0.782). All of the 5-FU2 doses show insignificant association with anemia severity. Just like with anemia onset, the only dose of cisplatin that show significant association with anemia severity was ≥ 1000 mg (P= 0.022; r = 0.819). Only the dose ≥ 110 mg docetaxel show significant association with anemia severity (P= 0.044; r = 0.997). As for the other chemotherapeutics drugs doses, they show insignificant association with anemia severity. However it is clear from the results that the association and correlation of chemotherapeutics drugs with anemia severity is greater than their association and correlation with anemia onset.

For Linear regression test results which show that 5-FU1 (which represent the bolus dose that given as a part of FEC regimen or 5-FU+ 5-FU regimen) ≥ 1000 mg has the strongest association and correlation with anemia onset (B= 779734.28, β= 0.973, P= 0.000), 900-999 mg (B= 66241.522, β= 0.811, P= 0.010), 800-899 mg (B= 3280.313, β= 0.751, P= 0.013), 700-799 mg (B= 271.014, β= 0.624, P= 0.029) and the other doses 600-699 and 400-599 show insignificant association. While for cyclophosphamide only ≥ 1000 mg (B= 84518.889, β= 0.884, P= 0.001) and 900-999 mg (B= 42800.856, β= 0.758, P= 0.045) while other doses show insignificant association with anemia onset. For epirubicin all of the doses show insignificant association with anemia onset. While for 5-FU2 (which is the second dose in 5-FU+ 5-FU regimen) i.e., the dose that given in the second day after the bolus dose of 5-FU1, only ≥ 700 mg show significant association (B= 269.385, β= 0.699, P= 0.033). For cisplatin only ≥ 100 mg show significant association with anemia onset (B= 313.637, β= 0.662, P= 0.032), also for docetaxel only ≥ 110 mg show significant association with anemia onset (B= 184.068, β=0.579, P=0.029). While for doses of other chemotherapeutic treatments used all show insignificant association with anemia onset.

While, for Linear regression test for chemotherapy doses with anemia severity, results also show that 5-FU1 (which represent the bolus dose that given as a part of FEC regimen or 5-FU+ 5-FU regimen) dose ≥ 1000 mg has the strongest association and correlation with anemia severity (B= 869276.53, β=0.992, P=0.000), 900-999 mg dose (B= 594760.22, β=0.847, P=0.023), 800-899 mg dose (B=56521.025, β=0.793, P=0.011), 700-799 mg (B= 331.117, β=0.661, P= 0.035) and the other doses 600-699 and 400-599 show insignificant association. While for cyclophosphamide only ≥ 1000 mg dose (B= 880793.07, β= 0.967, P= 0.009) and 900-999 mg dose (B= 84237.594, β= 0.811, P= 0.019) while other doses show insignificant association with anemia onset. For epirubicin all of the doses show insignificant association with anemia onset. While for 5-FU2 (which is the second dose in 5-FU+ 5-FU regimen) i.e., the dose that given in the second day after the bolus dose of 5-FU1, only ≥ 700 mg dose show significant association (B=307.419, β= 0.724, P= 0.043). For cisplatin only ≥ 100 mg dose show significant association with anemia onset (B=1077.369, β= 0.696, P= 0.036), also for docetaxel only ≥ 110 mg dose show significant association with anemia onset (B= 561.335, β= 0.626, P= 0.025). The results show stronger association and correlation of chemotherapeutic doses with anemia severity than its onset.

Discussion

As seen in the above statistical results that chemotherapy types association and correlated with anemia severity is greater than its association with anemia onset. It is also clear that FEC is highly associated and correlated with anemia onset and severity followed by 5-FU+5-FU or 5-FU then cisplatin then docetaxel. According to results of logistic regression, the type of chemotherapy most highly associated with anemia onset and severity were FEC, 5-FU plus 5-FU, Docetaxel and Cisplatin+5-FU.

The main explanation for this weak association with onset as compared with severity is that anemia prevalence increases with increase cycle of chemotherapy. Kosmidis and Krazakowski (2005) indicated that prevalence of anemia after chemotherapy treatment among lung cancer patients (solid cancer) increases progressively from 23.5% at cycle 1 to 77.3% at cycle 6.

Anemia as already known to be one of the main side effect of FEC regimen (Christie Hospital NHS Foundation Trust, 2008). Thus this could explain the high association of FEC with onset and severity of anemia found in this present study. Moreover Rodgers (2008) mentioned that breast cancer patients treated with a combination of 5-flurouracil and cyclophosphamide, a very myelosuppressive combination could cause

suppression even completing treatment for 5 years Rodgers also mentioned that this myelosuppressive effect will accumulate by repeating the cycles. So this can farther explain FEC regimen is highly and strongly associated with anemia onset and severity.

According to correlation and linear regression tests results which show that 5-FU1 (i.e., 5-FU first dose or bolus dose) dose ≥ 1000 mg has the strongest association and highest positive correlation with anemia onset and severity followed by doses of 900-999 mg then 800-899 mg and finally 700-799 mg. In the second rank came cyclophosphamide doses specifically ≥ 1000 mg and 900-999 mg which also show associations with anemia onset and severity. While for cisplatin only the dose ≥ 100 mg show significant association with anemia onset and severity and finally only ≥ 110 mg dose docetaxel show significant association with onset and severity. For all of the doses mentioned above, their association and correlations with severity were higher than that with the anemia onset.

The strong association between 5-FU dose (≥ 1000 mg) and anemia is because it is given as a bolus dose and bolus dose has been associated with severe myelosuppression of the bone so this can explain its high association and correlation with anemia onset and severity while 5-FU2 dose is not a bolus dose. Based on the 5-FU pharmacokinetic, the main side effect with boluse dose will be myelosuppression while if it is given in continues way its main side effect will be skin toxicity (Scur et al., 2005). Also Hamilton (2010) and Stephan (2010) indicated that one of the most common side effect of 5-FU chemotherapy is anemia (Hamilton, 2010. http://www.chemocare.com/BIO/fu.asp; Stephan, 2010. http://breastcancer.about.com/od/chemotherapydrugs/p/fluorouracil.htm.). Also for cyclophosphamide, docetaxel and cisplatin when given in high doses the main side effect will be suppression of the bone marrow (Howland and Mycek, 2006). In addition anemia and thrombocytopenia has been known to be mainly associated with cyclophosphamide dose and the incidence and severity can be reversed by reducing its dose (Drug Information Online, 2010. http://www.drugs.com/sfx/cyclophosphamide-side-effects.html). While in case of cisplatin the anemia happened because of its effect on kidneys which result in nephrotoxicity leading to reduction in EPO production which will cause anemia. The severity of this anemia mainly depend on cisplatin dose concentration since this concentration is proportional to nephrotoxicity severity. Also this also show that cisplatin dose concentration is related with anemia severity too (Wood and Hrushesky, 1995). Also a very important point mentioned by the American Society of Health System Pharmacist (2010) is that it has been proven that the incidence and severity of thrombocytopenia and neutropenia is related with cisplatin doses when it is more than 50 mg/ m2, however the relationship between anemia and cisplatin doses is still unclear (American Society of Health System Pharmacist 2010. http://www.medscape.com/druginfo/monograph?cid=med&drugid=8756&drugname=Cisplatin+IV&monotype=monograph&secid=4). So this present study then tries to find this relationship between cisplatin doses and anemia incidence and severity. The main finding that as the cisplatin dose is equal to 100 mg or higher will play critical role in incidence and severity of anemia. While the explanation for docetaxel based on the results of Ishmael et al. (2005) who conducted a study on 27 breast and lung cancer patients. He and his colleague used a revised protocol doses for combination of docetaxel and topotecan chemotherapy to get the main hematological and non-hematological side effects that will be associated with it. The main hematological side effects associated with these chemotherapeutics treatments were neutropenia, anemia and thrombocytopenia in different grades of severities, while incidence of non-hematological side effects happened within minority of the patients the most noticeable one was hair loses. Also, the main recommendation mentioned by this study was that the further studies should work to detect the optimal doses for each chemotherapy drug (Ishmael et al., 2005). While for its association with anemia as mentioned by Rang et al. (2003), docetaxel is a cell cycle specific chemotherapeutic agents so that kill many of highly proliferating cells like cancer cells and bone marrow cells thus leading to myelosuppression. Therefore neutropenia, anemia and thrombocytopenia are considered as common side effects (Rang et al., 2003). So this could explain the strong association observed between docetaxel doses and anemia onset and severity.

As mentioned earlier by Rodgers (2008), 5-flurouracil and cyclophosphamide combination can cause myelosuppression lasting even after 5 years of completing treatment (Rodgers, 2008). He also indicated that this myelosuppressive effect will accumulate with repeating cycles and it could also happen with short period of high dose intensity regimen observed in our present study whereby 5-FU was given in bolus dose and cyclophosphamide was given in high dose. So this could explain the reasons why these two agents are highly associated with anemia. The gemcitabine plus cisplatin combination has been proven to be more superior than cisplatin alone for the treatment of breast cancer but when its used it associated with a severe haematological toxicity i.e., anemia which need more blood transfusion (Vizor, 2005; Hamilton, 2010 http://www.chemocare.com/bio/cisplatin.asp).

The incidence and severity of anemia caused by chemotherapy depend on several factors mainly chemotherapy schedule, dose intensity and type of chemotherapy used (Rodgers, 2008). Thus, for the other chemotherapy treatment with insignificant results, the regimen may not intensive enough to cause significant bone depression and anemia. Also these regimens were not frequently used on patients as compared to the other 4 regimens that had shown significant association.

This part of the study is very important since as mentioned by Kirshner et al. (2004), information related with anemia associated with chemotherapeutics regimens used in early stages of breast cancer is still very scarce. So when this present study tries to elucidate these points not only in early stages of breast cancer but in many types of cancers it could be considered as a novel point.

The conclusion from this study is that FEC, 5-FU+ 5-FU, docetaxel and cisplatin+ 5-FU are considered as the

main risk factors which play a role in the incidence and severity of anemia and their association is greater with severity of anemia rather than onset of anemia. Moreover when the patients received ≥ 1000 mg or 900-999 mg dose for 5-FU or cyclophosphamide both doses are considered as a very critical factor inducing incidence of anemia and they are highly associated and correlated with increase in anemia severity. Also the same point but with a lower degree of severity happened when the patients received ≥ 100 mg cisplatin and ≥ 110 mg docetaxel. Therefore depending on the results of this present study, patients who are receiving these high doses regimens should be under close supervision in order to overcome the anemia that may arise.

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