RESEARCH COMMUNICATION

Treatment Patterns and Outcomes in Management of Solid Cancer Patients Suffering From Anemia in Penang Hospital

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Abstract

Introduction: Anemia is one of the most frequent hematological demonstration of malignant diseases, leading to impairment of function in all tissues and organs of cancer patients and associated with serious stress. This major problem may be exacerbated by radiotherapy or chemotherapy. It is characterized by lower hemoglobin (Hb) level or inadequate circulating red blood cells (RBCs). The present study evaluated the effectiveness of treatment guidelines for anemia among solid cancer patients in Penang hospital and to find associations between treatments and anemia onset and severity. Methods: This is a retrospective observational study was conducted on 534 cancer patients with anemia who were admitted to a government hospital on Penang island i.e., Penang General Hospital in the period between 2003 to 2009. Results: Effectiveness of standard anemia treatment guidelines was not sufficient because correction of anemia was just temporary. Conclusion: According to the results, erythropoietin must be used as a cornerstone even for patients who suffer from moderate anemia and blood transfusion should be used just for emergency cases when anemia leads to a critical situation.

Keywords: Anemia - solid cancers - treatment guidelines - erythropoietin

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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 5.4×10^6 cell/ μl and for female 4.8×10^6 cell/ μl (Haggerty, 1999; Blaser, 2001; Brown and Olde, 2005; Haut, 2007). It is considered as one of the most frequent hematological demonstration of malignant diseases, which will lead to momentous impairment in every tissues and organs of cancer patients and put them under serious stress.

Anemia may arise due to the underlining diseases (i.e., cancer diseases) or due to radiotherapy or chemotherapy treatment. This could be either myelosuppression which happened because of cancer metastasis to bone or because of chemotherapy or by inhibition of erythropoietin (EPO) synthesis by the kidney (i.e., inhibit erythropoiesis) or inhibition of EPO action on erythroid precursors leading to retention of iron in the reticuloendothelial system, gastrointestinal tract and hepatocytes or cytokine mediated failure of erythropoiesis. Anemia that occurs because of cancer it self is called anemia of chronic diseases (ACD) (Beguin, 2005; Means and McLaren, 2005; Haut, 2007; Blaser, 2001; Haggerty, 1999; Brown and Olde, 2005). Anemia and its related symptoms have serious negative effects on patients quality of life (QOL) and anticancer treatment since it will lead to treatment delay. The treatment strategies of anemia are mainly based on the clinical situation, clinical signs and symptoms and on the underlining cause of anemia. These treatments will include red blood cell transfusion, VitB12 and Epoetin alfa (recombinant human erythropoietin, rHuEPO). All these treatments were used to overcome anemia related signs, symptoms and to improve the anemic patients quality of life (QOL) (Pohl and Ludwig, 2005).

Several studies obligate future studies to clarify the benefits of anemia treatment guidelines, also the main effect of cancer growth-promoting effects on anemia and EPO should by carried out (Kitano et al., 2007; Khan et al., 2008;). Moreover Foubert, (2006) emphasized on the impoance of rewriting the guidelines by using the behaviorally specific terms and by consulting the consult board of specialist doctors in the specific hospital. This would thus increases the implementation of the guidelines. This process of reevaluating to ensure congruent of these guidelines with the needs for each area and hospitals or medical centers (Ludwing et al., 2009). The two main guidelines used in Penang hospital are very simple and abbreviated and not describing the proper ways to overcome and solve the anemia problem occurring in cancer patients. Also the guidelines do not contain the proper hemoglobin level to start the transfusion of blood or EPO administration and do not indicate the cases in

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which the chemotherapy treatment could be continued or delayed or reduced according to hemoglobin level (Guidelines for the rational use of blood and blood products; Chemotherapy protocol systematic therapy of cancer 2nd edition) (National Blood Centre Ministry of Health Malaysia, 2007; Ministry of Health Malaysia, 2007). For these reasons, this present study tries to evaluate the effect of treatment used for solid cancer patients suffering from anemia in Penang hospital and to find the association between these treatments and anemia onset and severity and to suggest additional information to the available guidelines for anemia treatment.

Materials and Methods

Study design and setting

This is a retrospective observational study, conducted in a government hospital on Penang island i.e., Penang 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). Approved 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).

This study tries to evaluate the effect of treatments used for solid cancer patients suffering from anemia in Penang hospital and to find the association between these treatments and anemia onset and severity and to suggest changes to the guidelines used for anemia treatment.

Data collection

Data was gathered 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. Patients suffering from hematological cancer or treated with radiotherapy or have an inherited problem with Hb or with pancreatic problem were excluded.

The variables collected in this part of the study include patient demographic data, types and stages of cancer diagnosed, Hemoglobin levels (Hb) before and after receiving chemotherapy, types of treatments used for anemic patients and effectiveness of each treatment (guideline).

The type of data collected includes categorical data which were non-normally distributed. This was confirmed with 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. In addition, this study is an observational study looking for association and thus this test was appropriate. 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%. Logistic regression test was used for data which shows significant results with Chi-square test so as detect which type or kind (guideline) of anemia treatment is highly association and correlated with anemia treatment. 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 with the highest Odd Ratio.

Results

Patient characteristics

The majority of the anemic patients (n=534) were women (n=336; 62.9%) with male representing only (n=198) 37.1%. Chinese were the predominant race (n=305; 57.1%), followed by Malay (n=178; 33.3%) and finally the Indian (n=51; 9.6%). Their mean age was 53.3 years (range, 18–93 years). Majority (n=148; 27.7%) were patients between 60-69 years old. Majority of the anemic patients suffered from breast cancer (n=186; 34.8%), followed by those with rectum cancer (n=64; 11.9%) and then came colon cancer 50 (9.4%). Most of them (n=349; 65.3%) suffered from early-stages disease and only a small number (n=185; 34.6%) had advanced-stage disease. One hundred and twenty six (126; 23.6%) of the total 534 patients suffered from anemia before receiving chemotherapy, while 408 developed anemia after receiving chemotherapy. Among the 408 patients majority of them were treated with fluorouracil, epirubicin and cyclophosphamide combination (FEC) (108; 26.5%) followed by those on 5-flurouracil+5-flurouracil (5-FU+ 5-FU) or 5-flurouracil (5-FU) (n=86; 21.1%) and docetaxel (n=42; 10.3%).

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. For those patients with anemia before chemotherapy, the results show that the majority of the patients (n=87; 69%) already has anemia when the diagnosis of cancer was first made, while in 39 (31%) patients their anemia were detected during the 2nd visit to the hospital after cancer was being diagnosed. Meanwhile 178 (43.6%) of the 408 patients who developed anemia after chemotherapy administration, do so after the 4th or more administration of chemotherapy. This is followed by those whose anemia was seen after the 3rd administration of chemotherapy (153; 37.5%), then those after the 2nd administration (n=75; 18.4%) and finally those after the 1st administration (n=2; 0.5%). Based on the Hb level, majority of the anemic patients suffered from moderate anemia (n=290; 54.3%) and followed by those with mild anemia (n=202; 38.4%). Only small proportion of the

Table 1. Effect of Anemia Treatment Guidelines on Hemoglobin Levels in Anemic Patients in Penang Hospital (n=534)

Treatment	N	Improvement	Hb level at 1st visit	Hb level at 2nd visit	Hb level at 3rd visit
Oral Iron	202	Supportive No signs	Maintain Hb unimproved	Reduction in Hb Signs start to appear there is a chance it may become moderate possibly postpone chemo	Anemia almost moderate Chemo postponed 2-3 days -
Blood + Iron	322	Fast temporary - improvement in Hb and signs	Temporary improvement Chance to postpone chemo	Unimproved Hb Slight Hb reduction anemic signs start to appear	Keep reducing Signs increase Chemo postpone for 2-3 days Blood given
Blood+ Iron + EPO	10	Significant improvement	Significant improvement in Hb (up to2g/ dL) Chemo on schedule	Maintain improvement Hb and signs clinical signs Chemo on schedule	Maintain improvement Chemo on schedule

patients suffered severe anemia (n=42; 7.8%). While for anemia treatment, majority of the patients received a combination of blood transfusion and oral iron (n=322; 60.3%) which is usually used for moderate and severe anemia, whereas 37.8 % (n=202) were treated with only oral iron. Finally came those who were treated with combination of blood transfusion+ EPO+ oral iron which is usually used for severe anemia with high risk.

Effect of anemia treatment on Hemoglobin level

The results (Table 1) show that the improvement in the hemoglobin level of the anemic patients treated were not very effective. This is because blood transfusion plus oral iron supplement only provide temporary improvement since by the time the patient returned for their second chemotherapy cycle the hemoglobin improvement was very little. Except in the case of erythropoietin (EPO), blood transfusion and oral iron supplement combination the test showed improvement in the Hb level.

The results of Chi-square test show insignificant association between type of anemia treatments with anemia onset before and after chemotherapy since P value was > 0.05, while the association with severity before and after chemotherapy showed significant association since the P value < 0.05.

The P values for the association of anemia treatment with anemia onset before chemotherapy is 0.624 and after chemotherapy is 0.451. While the P values of anemia treatment with anemia severity before chemotherapy is 0.021 and after chemotherapy is 0.036. For Logistic regression the results show that significant association exists between anemia treatment using oral iron plus blood transfusion with moderate anemia since P value equal 0.0202 but correlation with moderate anemia was weak since the odd ration is 0.621. Also significant association was found between oral iron with mild anemia since P value 0.032 and its odd ratio is 1.113. But insignificant association was observed between treatment with blood transfusion+ EPO+ oral iron and severe anemia since P value 0.816.

Discussion

The insignificant association obtained between anemia onset and anemia treatment is because these treatments were not started until the Hb level was reduced or until the patient was already anemic. This point has been also mentioned by Fathelrahman and Eman (2010) and Kosmidis and Krzakowski (2005) who reflect the results of European Cancer Anemia Services that the cancer patients do not receive their treatment until their Hb became low i.e., became anemic.

The logistic regression test was used to detect the degree of association and the factor most highly associated with treatment of anemia severity. The results of logistic regression show significant association between anemia treatment (blood transfusion plus oral iron) with moderate anemia. Also there was a significant association between oral iron supplement with mild anemia. On the other hand, the result shows insignificant association between anemia treatment with blood transfusion plus oral iron supplement plus EPO and anemia improvement. This could be due to very few patients treated with combination of blood transfusion plus oral iron supplement plus EPO. Whereas EPO should be the cornerstone even for those patients who were suffering from moderate anemia. So this could indicate that the treatment guideline used in general hospital of Penang need to be improved. This point has also been mentioned by Fathelrahman and Eman (2010) and Kosmidis and Krzakowski (2005) who confirm the results of European Cancer Anemia Services that the current treatment protocol is still lower than the optimal.

So the main recommendation for this present study is that the guideline must be improved. Therefore the treatment guideline being suggested by this study is to start using the oral iron supplement even before anemia develop and also before chemotherapy administration and focusing on using of erythropoietin (EPO) when Hb level drops to 10 g/ dL or lower in order to prevent blood transfusion which can be used only in emergency cases. This suggested guideline is based on the guideline developed by American Society of Hematology (ASH) and American Society of Oncology (ASCO) (Schwartzberg, 2007; Steensma, 2007; Ludwing et al., 2008; Cancer Consultants. com, 2010. http://professional.cancerconsultants.com/oncology_main_news.aspx?id=40846).

One of the critical points that support the suggestion of this present study to use the EPO is that solid cancer patients frequently suffer from reduction in EPO level as compared to their hemoglobin concentration. This reduction can be due to several factors such as the suppressive effect of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) which will lead to suppression of EPO synthesis. In

addition proinflammatory cytokines γ and β can blunt the erythropoiesis process which could then cause a blunt EPO response towards the low Hb level. Also chemotherapy plays a potent role in the incidence of anemia since it caused myelosuppression of the bone. While in case of hematological cancers, the patients would still have the appropriate EPO response towards anemia (Lappin et al., 2002; Beguin, 2005).

The main anemia treatment guidelines used by the Penang hospital are the guidelines for the Rational Use of Blood and Blood Products which has been produced by National Blood Centre/ Ministry of Health Malaysia and the Chemotherapy Protocol Systematic Therapy of Cancer 2nd edition. The Rational Use of Blood and Blood Products guideline deal with anemia caused by solid cancer in a very superficial way i.e., there is no mentioned of specific details regarding the uses, doses and treatment combination for anemia treatment. While it describe at length the part related with EPO use in treating anemia associated with renal failure. Similar information is found in the second guideline. So depending on the result of this study, suggestion to improve the guidelines is as follows.

1-The oral iron supplement should be started even if the cancer patient does not suffer from anemia and before the initiation of chemotherapy.

2-The use of EPO should be started when Hb dropped to 10 g/ dL or lower and to reduce the use or the dependence on blood transfusion which is used in emergency cases only.

3-But a very important point is that the EPO level of the cancer patients must be evaluated before it is being use. The normal range of EPO is between 6-32 U/ L about (10-11 mol/ L). When anemia happens the EPO level will increase exponentially so when the EPO level is above 100 mU/ mL, EPO administration should not be used.

4-The initial dose of EPO should be 150 U/ kg three times a week for a minimum of 4 weeks. When the Hb response is weak i.e., < 1-2g/ dL increases in Hb concentration then the EPO doses should be increases to 300 U/ kg three times a week for another 4-8 weeks. The use of EPO should be stop when Hb level reach to about 12 g/ dL.

5-The use of combination of EPO plus oral iron supplement is allowable and there is no problem with the uses of these two agents together. The uses or the addition of blood transfusion to this combination is considered necessary only when Hb level is lower than 9 g/ dL or lower or when the response to EPO use is lower than expected.

So this study concluded that EPO must be used as a cornerstone for treatment of anemia caused by solid cancer diseases and blood transfusion should only be used in emergency cases i.e., when anemia can lead to a critical situation.

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