RESEARCH COMMUNICATION

Treatment Patterns and Outcomes in Management of Solid Cancer Patients Suffering from Thrombocytopenia in Penang Hospital

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Abstract

Introduction: Thrombocytopenia denotes abnormal decreases in platelet numbers and is a major detrimental side effect of the chemotherapy or cancer disease itself which cal lead to hemorrhage from vital organ. This is particularly a problem for the brain specifically within solid cancer patients and has a great negative effect on cancer patients quality of life (QOL). It ranges from mild bleeding from small blood vessels to severe bleeding from large blood vessels. The present study was conducted to evaluate the effectiveness of treatment guidelines for thrombocytopenia among solid cancer patients in Penang hospital and to find associations between these treatments and thrombocytopenia onset and severity and to suggest changes in the guidelines. Methods: This retrospective observational study, conducted in a government hospital on Penang island included 341 cancer patients with thrombocytopenia who were admitted in the period between 2003 to 2009. The main statistical tests used were Chi-square test and Logistic regression test. The level of significance was set at $P < 0.05$. Results: Of the total of 341, 21 (6.2%) showed thrombocytopenia before receiving chemotherapy and the remaining 320 (93.8%) after chemotherapy. The majority suffered from moderate thrombocytopenia (n=172; 53.8%), followed by mild a (n=97; 30.3%) and finally severe (n=51; 15.9%). For treatment, chemotherapy was delayed/ reduced (n=223; 65.4%) or platelets were transfused (n=51; 34.6%). However, thrombocytopenia problems were only temporarily solved. Conclusion: Effectiveness of thrombocytopenia treatment guidelines was found to be insufficient. It is advisable that thrombopoietin be used as a cornerstone even for patients who suffer from moderate thrombocytopenia and platelets transfusion should be used just for emergency cases when thrombocytopenia leads to a critical situation.

Keywords: Treatment guidelines - thrombocytopenia - solid cancer - Malaysia

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Introduction

Thrombocytopenia an abnormal term used to denote abnormal decreases or drop in platelets numbers. Thrombocytopenia is a common problem experience by cancer patients, which usually results from the use of conventional chemotherapy and at times is a dose limiting factor for chemotherapy administration. The incidence of thrombocytopenia among solid cancer patients is rather low i.e., ranging between 10%-25% among breast cancer, ovarian and germ cell cancer patients who were treated with intensive chemotherapy. However thrombocytopenia incidence is high among acute leukemia patients (De Bellis, 1999; Dolan, 2000; Elting et al., 2001; Cantor et al., 2003; Dolan, 2005; Miller and De Bellis, 2005; Kuter, 2006; Terranova et al., 2007). Chemotherapies can cause thrombocytopenia by different mechanisms i.e., either by suppressing megakaryopoiesis which is the process of proliferation and maturation of immature megakaryocyte so this will lead to prevention of platelets production or by direct damage of the platelets. Also they may cause bone marrow suppression this will reduce bone marrow production for the platelets. Solid cancer produce thrombocytopenia mainly by metastasis to bone marrow, which is mainly and specifically seen in breast, prostate and lung cancers (De Bellis, 1999; Dolan, 2000; Miller and De Bellis, 2005).

There are different options for treatment of thrombocytopenia but the treatment selection will mainly depends on the cause or etiology and severity of thrombocytopenia. If the cause is chemotherapy then it need to be either to continue the treatment with lower chemotherapy doses or by using alternative drugs or to use platelets growth factors (i.e., thrombopoietic growth factor) (TPO). TPO such as recombinant human interleukin-11 (rhIL-11) will be used at the dose of for adult

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patient dose 50 μg/ kg/ day and pediatric dose is (75 μg/ kg/ day) in order to which will stimulate megakaryocyte maturation and proliferation for maintaining platelets production. It has been proven by the Food and Drug Administration (FDA) that rhIL-11 is very effective in reducing and prevention of severe thrombocytopenia as well as it will decrease the need for platelet transfusions especially after myelosuppressive chemotherapy which could be continue with the same doses.

In the case of severe thrombocytopenia caused by intensive cancer chemotherapy (i.e., platelet level ≤ 20,000/ μL) platelets transfusion is needed for prevent any bleeding complication. But in clinical setting the there are some limitation to its use which are the availability of the blood products since it must be freshly taken and used within 5 days, cost, refractoriness, transfusion reaction and diseases transmission (De Bellis, 1999; Dolan, 2000; Demetri, 2001; Wandt et al., 2001; McFarlane-Parrott, 2002; Cantor et al., 2003; Milman et al., 2003; Miller and De Bellis, 2005). According to American Society of Clinical Oncology (ASCO) the development and the production for the new guideline will be done by reviewing literatures using systematic grading of the evidence and also by incorporating expert opinion since the patients clinical circumstances are very important to decide the type of treatment or guideline to be used (Schiffer et al., 2001).

The two main guidelines used in Penang hospital are very simple and abbreviated. Furthermore they do not describing the proper ways to overcome and solve thrombocytopenia incidence occurring in cancer patients. Besides that the current guidelines do not explain the proper platelets level to start the transfusion of platelets administration and do not indicate the cases in which the chemotherapy treatment could be continued or delayed or reduced according to platelets 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 thrombocytopenia in Penang hospital and to find the association between these treatments and thrombocytopenia onset and severity and to suggest additional information to the available guidelines for thrombocytopenia treatment.

Materials and Methods

Study design and setting

This is a retrospective observational study at Penang General Hospital which is located in the state of Penang Island. Penang Hospital is the biggest public hospital in north Malaysia and it is the major referral center for cancer patients in main region of Malaysia. The ethical approval for the the conduction of the study was obtained from Clinical Research Centre (CRC) of , Ministry of Health Malaysia (MOH).

The main objectives of this study are to evaluate the effect of treatments used for solid cancer on the occurrence of thrombocytopenia and to find the association between these treatments and thrombocytopenia onset and severity. Based on the outcome of this study, specific recommendation will be made for changes the present guidelines for treatment of thrombocytopenia.

Study Population

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

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 thrombocytopenia were chosen.

Any thrombocytopenic patient suffers from hematological disease, or treated with radiotherapy were excluded. Any patients with immune thrombocytopenic purpura (ITP) or autoimmune disease or thromboembolic disease or active infection required an antibiotic treatment or leukemia or stem cell or bone transplantation were excluded. Also any patient who suffer from arterial arrhythmias or congestive heart problem or any surgical operation on any vital body organ which may effect on platelets level were also excluded (World Health Organization, 2010).

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

Statistical analysis

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 to detect which type or kind (guideline) of thrombocytopenia treatment is highly association and correlated with 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 odds ratio.

Table 1. Prevalence of Thrombocytopenia Among Solid Cancer Patients

Thrombocytopenia variables	Value
Thrombocytopenia presence (n=341)	
Before chemotherapy	21 (6.2%)
After chemotherapy	320 (93.8%)
Onset of thrombocytopenia before chemotherapy (n=126)	
1st diagnosis (1st visit to hospital)	16 (76.2%)
2nd diagnosis	5 (23.8%)
Onset of thrombocytopenia after chemotherapy (n=408)	
1st cycle	2 (0.6%)
2nd cycle	57 (17.8%)
3rd cycle	121 (37.8%)
4th and more cycle	140 (43.8%)
Severity of thrombocytopenia (platelets levels) (n=341)	
$< 150 - \geq 100 \times 10^3$ / mL	118 (34.6%)
$< 100 - \geq 50 \times 10^3$ / mL	172 (50.4%)
$< 50 - > 20 \times 10^3$/ mL	37 (10.9%)
$\leq 20 \times 10^3$ / mL	14 (4.1%)
Thrombocytopenia treatment (n=341)	
No treatment (chemo continue)	67 (19.6%)
Chemo delayed	223 (65.4%)
Chemo delayed+ reduced +platelets	51 (15%)

$< 150 - \geq 100 \times 10^3$ / mL = mild, $< 100 - \geq 50 \times 10^3$ / mL = moderate, $< 50 - > 20 \times 10^3$/ mL= minor bleeding (severe), $\leq 20 \times 10^3$ / mL = major bleeding (severe).

Results

Patient characteristics

TThe majority of the thrombocytopenic patients (n=341) were women (n=216; 63.3%) with male representing only (n=125) 36.5%. Chinese were the predominant race (n=200; 58.6%), followed by Malay (n=105; 30.8%) and finally the Indian (n=36; 10.6%). Their mean age was 52.4 years (range, 20–81 years). Majority (n=104; 30.5%) were patients between 50-59 years old. Majority of the thrombocytopenic patients suffered from breast cancer (n=121; 37.8%), followed by those with colon cancer (n=54; 16.9%) and then followed by ovarian cancer 43 (13.4%). Most of them (n=214; 62.8%) suffered from early-stages disease and only a small number (n=127; 39.7%) had advanced-stage disease. 21 (6.2%) of the total 341 patients suffered from thrombocytopenia before receiving chemotherapy, while 320 developed thrombocytopenia after receiving chemotherapy. Among the 320 patients majority of them were treated with fluorouracil, epirubicin and cyclophosphamide combination (FEC) (n=72; 22.4%) followed by those on 5-flurouracil+5-flurouracil (5-FU+ 5-FU) or 5-flurouracil (5-FU) (n=59; 18.4%) and FOLFOX (n=33; 10.3%).

Prevalence of thrombocytopenia

For those patients with thrombocytopenia before chemotherapy, the results show that the majority (n=16; 76.2%) already has thrombocytopenia when the diagnosis of cancer was first made, while in 5 (23.8%) patients their thrombocytopenia were detected during the 2nd visit to the hospital after cancer was being diagnosed. Meanwhile 140 (43.8%) of the 320 patients who developed thrombocytopenia after chemotherapy administration, do so after the 4th or more administration of chemotherapy. This is followed by those whose thrombocytopenia was seen after the 3rd administration of chemotherapy (121; 37.8%), then those after the 2nd administration (n=57; 17.8%) and finally those after the 1st administration (n=2; 0.6%). Based on the platelets level, majority of the thrombocytopenic patients suffered from moderate thrombocytopenia (n=172; 53.8%) and followed by those with mild thrombocytopenia (n=97; 30.3%). Only small proportion of the patients suffered from severe thrombocytopenia (n=51; 15.9%) that is those who suffer from low severity with minor bleeding (n= 37) while the rest 14 patients suffer from major bleeding. While for thrombocytopenia treatment, majority of thrombocytopenic patients were treated with only chemotherapy delayed (n=223; 65.4%) which is usually used for those who suffered from moderate thrombocytopenia and severe thrombocytopenia, whereas 14.9 % (n=51) were treated with platelet transfusion and delayed or reduced chemotherapy and these were patients who suffer from severe thrombocytopenia. While those who suffer from mild thrombocytopenia received nothing and their chemotherapy continued and not reduced. All these variables are shown in Table 1.

Effect of thrombocytopenia treatment on platelets level

This part of the study looks at the effect of the treatments which is based on the treatment guidelines of thrombocytopenic patients in Penang hospital and is shown in Table 2.

The results show that the improvement in the platelets level of the thrombocytopenic patients treated were not very effective. This is because platelets transfusion plus chemotherapy delayed and reduced only provide temporary improvement since by the time the patient returned for their second chemotherapy cycle the platelets improvement was very little.

Inferential statistical analysis

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

The P values for the association of thrombocytopenia treatment with thrombocytopenia onset before chemotherapy is 0.691 and after chemotherapy is 0.919. While the P values of thrombocytopenia treatment with thrombocytopenia severity before chemotherapy is 0.471 and after chemotherapy is 0.011. All these information shown in Table 3. For logistic regression the results show that significant association exists between thrombocytopenia treatment using chemotherapy delayed with moderate thrombocytopenia since P value equal 0.048 but correlation with moderate thrombocytopenia was weak since the odd ration is 0.015. But insignificant association was observed between treatment with chemotherapy delayed and reduced with severe thrombocytopenia since

Table 2. Effect of Thrombocytopenia Treatments Guidelines on Platelets Level for Thrombocytopenic Patients in Penang Hospital (n=341)

Kind of Treatment	N	Improvement	Plt 1st visit	Plt 2nd visit	Plt 3rd visit
Chemo delayed	223	Temporally	Temporally	-Mild thrombo -No signs -Chemo may delayed	-Platelet level keep reducing -Chemotherapy delayed again
Platelets, Chemo delayed and reduced	51	Significant improved temporally	-Slight reduction within platelets level chemo continue -Chemo continue	-Mild thrombo -No signs -Chemo may be delayed	-Significant thrombo with signs and -Chemo delayed again
Total	274				

Table 3. Logistic Regression Analysis of Treatment with Thrombocytopenia Severity After Chemotherapy

Variable	P	Odds Ratio	95% CI
Treatment with thrombocytopenia severity after chemo	0.031		
1 Chemotherap Delayed	0.048	0.015	0.071-5.067
2 Chemotherapy Delayed + reduced	0.069	0.031	0.011-4.114
3 Platelet Transfusion	0.351	0.187	0.161-5.128

P value 0.069. Same result of insignificancy between platelets transfusion with severe thrombocytopenia since P value 0.351.

Discussion

The incidence of thrombocytopenia in solid cancer patients with or without chemotherapy treatment is well established but in most of the studies reviewed. But this present study consider as the first study in Malaysia which works on to evaluate the effectiveness of thrombocytopenia treatment guideline with onset and severity of thrombocytopenia. Furthermore, it consider the first study in Malaysia which works on to built a specific guideline for treatment of thrombocytopenia within solid cancer patients. The insignificant association between thrombocytopenia onset and treatment is because these treatments were not used until the platelets level were already below normal i.e., patient became thrombocytopenic.

The results of logistic regression show a significant association exists only between chemotherapy delayed with thrombocytopenia treatment and chemotherapy delayed used only for moderate thrombocytopenia. But this association is very week depending on the results of logistic regression which show a very week relation since the odd ratio is very small. This point has been proved by following the platelets level within the three laboratory checks which show that chemotherapy delayed just lead to slight improvement in platelets level and that improvement did not continue for long time i.e., just temporally.

According to Vadhan-Raj (2009) and Elting et al. (2001) who indicated that the chemotherapy delayed when used to treat thrombocytopenia of solid cancer patients was characterized by low clinical outcome and when compared with chemotherapy dose reduction found that dose reduction was better than dose delayed in thrombocytopenia treatment. But chemotherapy doses reduction is associated with some of the serious problems. Like in breast cancer patients when chemotherapy doses were reduced to less than 85% of the targeted doses this will lead to significant decreased in the relapse of free survival period.

It has been reported by Vadhan-Raj (2009) that one of the rapid and effective treatment for thrombocytopenia is by using platelet transfusion. But it consider as a temporal solution and present study conducted confirm this result.

Besides that platelets transfusion is usually associated with many problems firstly the high cost, possibility of transfer infection, patient can experience immunogenic reaction and patient may be refractory to platelet transfusion.

Vadhan-Raj (2009) mentioned that thrombocytopenia treatment should mainly depend on thrombopoietin (TPO) administration in order to reduce platelets transfusion, also TPO can be administered in combination with chemotherapy drugs in order to prevent incidence of severe thrombocytopenia. But the main point has mentioned by Vadhan (2009) was that it is required to detect TPO optimal dosage and schedule of administration.

Li et al. (2007) conducted a study on 76 gastrointestinal cancer patients whom suffers from severe thrombocytopenia (platelets level were lower than 75 × 109/ L). Patients were treated with a rh-IL11 dose of 25 μg/ kg/ day for about 7-14 days until their platelets levels were more than or equal to 100 × 109/ L. The main results of the study showed that the used of rh-IL11 was very effective since the patients who receive it required just 8.9 days to recover while those who did not received rh-IL11 required 12.9 days. Besides that this study obligate on the safety of rh-IL11 in the treatment of thrombocytopenia that taken place among solid cancer patients.

The main thrombocytopenia 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 only mention the treatment of thrombotic thrombocytopenic purpura (TTP) in pregnancy but it does not cover the management protocol for thrombocytopenia caused by cancer or chemotherapy. Similar information is found in the second guideline.

Moreover one of the supportive points which show and clarify the importance of this present study which mentioned by Psaila and Bussel (2007). That

the utility of TPO agents in attenuating the severity of thrombocytopenia and reducing the need for platelets transfusion within thrombocytopenia cases that taken place after chemotherapy treatment, is still less clear-cut i.e., still unclear. This present study tries to clear that effect through Table 2 since it will show the weak action for the treatment guidelines that used in general hospital of Penang which do not contain TPO.

Based on the result of this study, suggestions to improve the guidelines can be made as following:

1-The need for doing laboratory blood test i.e., checks up for platelets level before starting chemotherapy cycle must be carried out.

2-Chemotherapy delay protocol should be used in case of mild thrombocytopenia (i.e., platelets > 50,000/ μL) only and the maximum delay period should be for 1 or 2 weeks only. When platelets < 50,000/ μL then chemotherapy must be delay and dose reduction will be used but reduction should not exceeded 15%.

3-When platelets < 50,000/ μL, TPO regimen is preferred to be used in order to prevent incidence of severe thrombocytopenia and to reduce and/ or prevent platelets transfusion.

4-TPO such as Oprelvekin should be administrated in dose of 50 μg/ kg/ day subcutaneously in case of patients who does not suffer from severe renal impairment and in a dose of 25 μg/ kg/ day in patient with severe renal impairment.

5-Platelets transfusion will be used only in case of emergency bleeding since it is consider as the most active and rapid way to treat patients with severe thrombocytopenia (Vadhan-Raj , 2009).

6-Solid cancer patients who are consider as highly prone to incidence of thrombocytopenia are those who suffer from beast, colon, gynecological, lung and prostate cancers specifically those in the third and more stages. Other types of solid cancers also can cause thrombocytopenia but those mentioned above are the most predominant.

7-Physicians and clinicians should highly focus on cancer patients who received FEC and 5-FU-FU or 5-FU, cisplatin-5-FU and docetaxel, docetaxel-cisplatin, FOLFOX, gemcitabine-cisplatin and gemcitabine regimens.

8-The incidence of thrombocytopenia is high after the third and more cycles of the above mentioned chemotherapy regimens.

9-Moreover, physicians and clinicians focuses must give more attention on patients who were treated with 5-FU dose ≥ 900, cyclophosphamide doses ≥ 1000 and cisplatin dose ≥ 100 mg since they are prune to thrombocytopenia.

So this study concluded that the TPO is warranted in certain cases and it must be used as a cornerstone for treatment of thrombocytopenia caused by solid cancer diseases or chemotherapy treatment and platelets transfusion should only be used in emergency cases i.e., when bleeding can lead to a critical situation.

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