RESEARCH ARTICLE

Factors Potentially Associated with Chemotherapy-induced Anemia in Patients with Solid Cancers

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Abstract

Purpose: Chemotherapy-induced anemia (CIA) is one of the most important causes of anemia in cancer patients. This study was conducted to describe the prevalence and characteristics of CIA in solid cancer patients in the Chinese population, and to explore the relationship of white blood cell (WBC) or platelet decrease with CIA. Methods: Data on age, gender, tumor diagnosis, anti-cancer treatment and blood cell analyses were available from 220 untreated non-anemic cancer patients who received at least 2 cycles of chemotherapy, and the data were analyzed to assess their relationship with CIA or its severity. Results: 139 patients (63.2%) presented anemia, most being Grade 1 or 2. Esophageal and lung cancers were associated with a high prevalence. G3/4 leucopenia and decrease of platelets were identified as independent risk factors for the occurrence of CIA. Moreover, G3/4 leucopenia, decrease of platelet and G3/4 thrombocytopenia were found to be also associated with the severity of CIA. Cisplatin-containing regimens were a main potential factor in causing CIA, although significant association was only found on univariate analysis. Conclusion: Anemia or decrease in hematoglobin are common in Chinese cancer patients receiving chemotherapy. Cisplatin-containing regimens might be an important factor influencing the occurrence of CIA. Our analysis firstly described some risk factors, such as decrease of platelets or WBCs, severity of leucopenia or thrombocytopenia, associated with the occurrence and severity of CIA.

Keywords: Chemotherapy-induced anemia - cancer - cisplatin - leucopenia - thrombocytopenia

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Introduction

Cancer is one of the most frequent conditions associated with anemia of chronic disease (Weiss et al., 2005), meantime, anemia is a common complication of cancer (Wilairat et al., 2012). The causes of anemia in cancer patients are multifactorial and chiefly identify as the malignant disease process itself and/or its iatrogenic therapeutic procedures (Steensma, 2008; Hassan et al., 2011). The estimated prevalence of anemia varies ranging from 30% to 90% of cancer patients during the course of their diseases (Knight et al., 2004; Achariyapota et al., 2010). A large prospective survey including 15367 cases from European Cancer Anemia Survey (ECAS) indicated that the prevalence of anemia at enrollment was 39.3% and 67.0% during the survey (Ludwig et al., 2004). In our prior analysis of 1133 newly diagnosed solid cancer patients, the prevalence of anemia at diagnosis in Chinese population was 18.98%. Additionally, aged, decreased food intake, and bleeding history were identified as independent risk factors for anemia occurrence at diagnosis in this group (Gao et al., 2011).

While the prevalence is even higher in patients receiving chemotherapy or radiotherapy (Hassan et al., 2011), particularly cytotoxic chemotherapy is considered as one of the most important causes of anemia in cancer patients, and the severity of anemia depends on the extent of disease and the intensity of treatment (Hassan et al., 2011). It is estimated that approximate 800,000 (61%) of the 1.3 million cancer patients in the United States who are receiving chemotherapy are anemic (Tchekmedyian, 2002). The incidence and severity of anemia in malignant diseases depends on the type of underlying malignancy, the stage and duration of the disease, the regimen and intensity of tumor therapy (Mercadante et al., 2000; Hassan et al., 2011). The anemia-related symptoms can have a profound negative impact on quality of life (QOL) for cancer patients (Aapro et al., 2012), moreover, anemia is associated with shorter survival times for patients with almost all types of cancer (Caro et al., 2001; Pongsanon et al., 2011).

To predict the development of chemotherapy-induced anemia (CIA) and allow for earlier measures to effectively manage anemia and prevent anemia complications, initial hematoglobin (HB) level, cancer type, whether treatment with platinum, and age, gender were identified

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as significant predictive factors in some studies (Barrett-Lee et al., 2006), however, data in Chinese patients is sparse. Previously, we reported the prevalence of anemia at diagnosis in a Chinese group of newly diagnosed solid cancer patients (Gao et al., 2011). Here, we reported the prevalence and characteristics of CIA in non-anemic subgroup of these patients who thereafter received chemotherapy, and we also tried to explore the relationship of the decrease in white blood cell (WBC) and platelet with CIA in these patients.

Materials and Methods

Study Population

1133 patients' computer-based record data in our hospital during January 2010 to May 2011 as shown in our previous report (Gao et al., 2011) were screened. Inclusion criteria were: male or female aged 18 years or over; histologic or cytologic confirmation of solid tumors; the cancers were firstly diagnosed without prior antitumor therapy; no anemia at cancer diagnosis (HB for male ≥ 120 g/L and for female ≥ 110 g/L); thereafter received at least 2 cycles of chemotherapy with or without radiation therapy in our hospital; had complete data of medical history and treatment records; blood parameter test, within 2 weeks before the treatment, at least once a week during the chemotherapy, and at least once a month after treatment till six month after the initiation of chemotherapy, were required for qualification.

The exclusion criterions were as following: a history of diseases of hematological system (including hematological malignancies) or bone marrow, or anemia of all causes, or chronic renal diseases; those received blood transfusion, ESAs, or iron supplementation < 3 months before the cancer diagnosis; obvious bleeding during the course of treatment.

Data Collection

Collected data included age, gender, the diagnosis and stage of the cancers, the locations of metastasis, chemotherapy and radiotherapy regimen, the parameters of blood cell count analysis. HB level at the start of cycle 1 was considered baseline, the appearance time, the severity and the types of anemia, and the severity of leucopenia or thrombocytopenia were recorded.

Anemia, leucopenia, thrombocytopenia and their grades were regarded according to National Cancer Institute (NCI) anemia scale from Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The definition of anemia was HB concentration < 120 g/L for male and < 110 g/L for female. The grades of anemia were divided into grade 1 to 4. 100 g/L ≤ HB < lower limit of normal (LLN) was considered as degree 1, 80 g/L ≤ HB < 100 g/L as degree 2, 65 g/L ≤ HB < 80 g/L as degree 3, and HB < 65 g/L as degree 4 (Groopman et al., 1999).

Statistics Analysis

Where appropriate, the univariate statistical analyses between dichotomous variables were determined by the Pearson chi-square or Fisher's exact tests to compare the CIA occurrence and severity in separate groups. The two independent samples nonparametric test was undergone meantime to analyze the association between severity of anemia and the respective variable. Binary logistic regression analysis was used to identify potential associated risk factors for prevalence of CIA. SPSS statistics (version 13.0) was used for all analyses.

Results

The Prevalence Rate of CIA

From 1133 new diagnosed cancer patients previously reported by us (Gao et al., 2011), 220 non-anemic patients who received chemotherapy met the inclusion criteria and were enrolled for this analysis, including lung cancers (76 cases), gastrointestinal cancers (28 cases, gastric or colorectal carcinomas), esophageal carcinomas (22 cases), nasopharyngeal carcinomas (24 cases), breast cancers (53 cases), and others (17 cases). Total 1009 cycles (range 2 to 12, median 4) of cytotoxic chemotherapy were performed. The median age in the 220 patients was 55. Of these patients, 65 patients received palliative chemotherapy for their metastatic diseases, the remaining 155 patients received adjuvant or radical chemotherapy and/or radiotherapy.

Totally, anemia was observed in 139 of the 220 patients (63.2%). The prevalence of CIA in different tumors was shown in Figure 1. Over 80% of the patients with esophageal or lung cancers had anemia during the treatment. The occurrence of CIA was found to increase with the cycles of chemotherapy (Figure 2). Majority of the 139 anemic patients presented anemia in their first 3 cycles, and all anemia was found during their first 6 cycles. There was no difference in cycles of chemotherapy

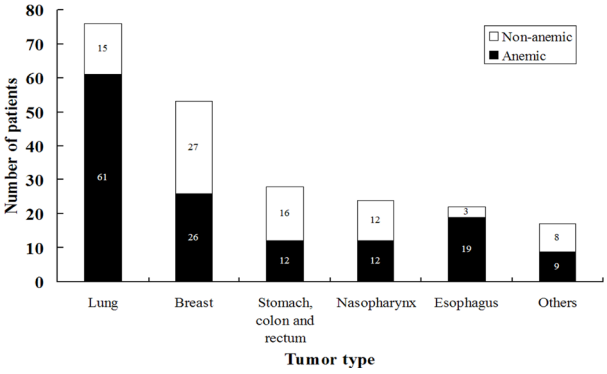

Figure 1. Prevalence of CIA in Different Types of Cancer

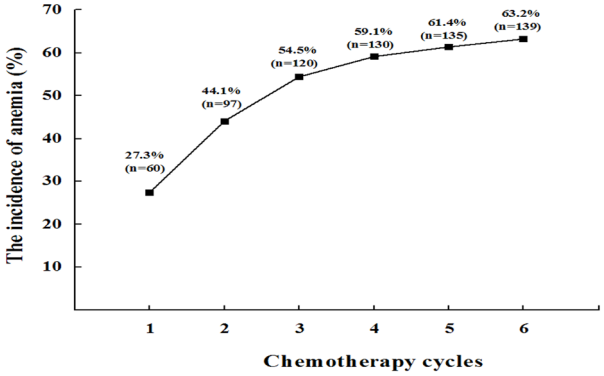

Figure 2. The Occurrence of CIA During Chemotherapy Cycles

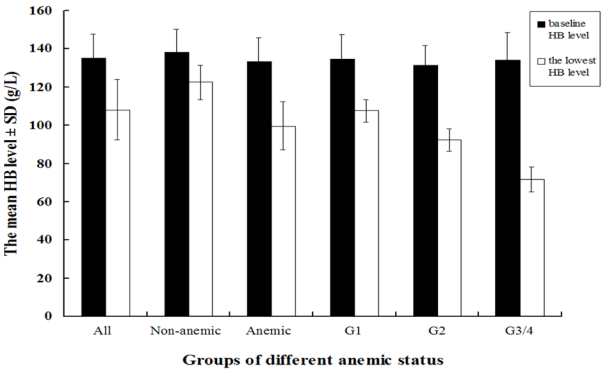

Figure 3. The HB Level Before Chemotherapy and the Lowest Level Afterward

Table 1. The Prevalence and Severity of CIA

Grade (HB)	No. of patients	No. of chemotherapy cycles (range, median, mean)	Prevalence of anemia (%)
Non-anemic	81	389 (2-12, 4, 4.8)	-
Anemic	139	620 (2-9, 4, 4.46)	63.2 (139/220)
G1 (100g/L~LLN*)	82	371 (2-9, 4, 4.52)	37.3 (82/220)
G2 (80~100g/L)	45	190 (2-7, 4, 4.22)	20.5 (45/220)
G3/4 (<80g/L)	12	59 (2-8, 4.5, 4.92)	5.5 (12/220)

*LLN= lower limit of normal HB = 120 g/L for male and = 110 g/L for female

between CIA and non-CIA groups.

The CIA prevalence of the patients was described respectively according to the grade of anemia group. Majority of the 139 anemic patients were mild or moderate anemia (Grade 1/2), the Grade 3/4 anemia was found in 5.5% of patients, as Table 1 showed. There was no significant difference in initial HB level before chemotherapy among groups. Although 139 patients were diagnosed to be anemic, most of non-CIA patients (93.8%) also experienced the various decrease in HB (Figure 3).

The relevant index about blood cell parameter of the most serious CIA (the lowest HB overall) during the course of treatment in the 139 anemic patients was as following: the mean RBC, 3.42±0.57 (1.89-5.54) L/L; the mean HCT, 0.303±0.041 (0.2-0.38) L/L; the mean MCV, 89.48±6.35 (65-104.8) fL. 89.9% of the CIA patients presented as normocytic anemia, and microcytic anemia (6.5%) and macrocytic anemia (3.6%) were also observed.

Determining the Associated Risk Factors for CIA

To explore the potential risk factors for CIA, CIA and non-CIA patients were compared to analyze the relationship of their characteristics and anemia occurrence (Table 2). We found male patients got more probabilities for CIA than female (79.5% v.s. 54.1%, P = 0.012, OR = 2.028, 95%CI 1.163-3.537), and the patients aged 60 years or older were susceptible to CIA than those aged below 60 (76.9% v.s. 57.4%, P = 0.006, OR = 2.472, 95%CI 1.279-4.778). Cisplatin-containing regimen resulted in more anemia than non-cisplatin chemotherapy (75.2% v.s. 52.9%, P = 0.001, OR = 2.702, 95%CI 1.516-4.815). The patients with decreased WBC were found to have more occurrence of anemia than those without (69.4% v.s. 40.4%, P = 0.000, OR = 2.337, 95%CI 1.714-6.496). Furthermore, G3/4 leucopenia strongly indicated anemia occurrence than other patients, and the prevalence rate was 94.8% and 51.9% respectively (P = 0.000, OR = 17.024, 95%CI 5.116-56.646). The decrease in platelet was also found to be associated with anemia than normal platelet (84.5% v.s. 50.0%, P = 0.000, OR = 5.462, 95%CI 2.767-10.782). G3/4 thrombocytopenia also powerfully showed more anemia occurrence than other patients (100% v.s. 59.9%, P = 0.001, OR = 1.664, 95%CI 1.487-1.861). Although the patients receiving radiotherapy have a relatively higher rate of anemia, no significant difference was found.

Table 2. Relationship Between Prevalence of CIA and Potential Associated Factors

Factors	Anemia	Non-anemia	Total	χ^2	P-value
Gender					
Male	86(70.5%)	36(29.5%)	122	6.291	0.012
Female	53(54.1%)	45(45.9%)	98		
Age					
≥60	50(76.9%)	15(23.1%)	65	7.489	0.006
<60	89(57.4%)	66(42.6%)	155		
Regimen					
Cisplatin containing	76(75.2%)	25(24.8%)	101	11.686	0.001
Non-cisplatin	63(52.9%)	56(47.1%)	119		
Radiotherapy					
Yes	46(69.7%)	20(30.3%)	66	1.72	0.190
No	93(60.4%)	61(39.6%)	154		
Decrease in WBC					
Yes	120(69.4%)	53(30.6%)	173	13.305	0.000
No	19(40.4%)	28(59.6%)	47		
G3/4 leucopenia					
Yes	55(94.8%)	3(5.2%)	58	33.909	0.000
No	84(51.9%)	78(48.1%)	162		
Decrease in platelet					
Yes	71(84.5%)	13(15.5%)	84	26.606	0.000
No	68(50.0%)	68(50.0%)	136		
G3/4 thrombocytopenia					
Yes	17(100%)	0(0)	18	10.736	0.001
No	122(60.1%)	81(39.9%)	202		

Potential associated factors (gender, age, regimen, radiotherapy, decrease of WBC, G3/4 leucopenia, decrease of platelet, G3/4 thrombocytopenia) were included for analysis of independent risk factors by stepwise logistic regression analysis. Ultimately, G3/4 leucopenia and decrease in platelet were identified as independent risk factors by both forwards and backwards stepwise logistic regression analysis.

Determining the Associated Risk Factors with the Severity of CIA

To analyze possible risk factors associated with the severity of anemia, the patients with CIA were divided into three groups (grade 1, G1; grade 2, G2; and grade 3/4, G3/4) according to the NCI anemia scale. G3/4 leucopenia, decrease of platelet and G3/4 thrombocytopenia were considered to be also associated with the severity of CIA, the chemotherapy regimen was found to have association by the two independent samples nonparametric test. The patients with decreased platelet, G3/4 thrombocytopenia or G3/4 leucopenia suffered more moderate and severe CIA than the patients without, who more presented mild anemia. Furthermore, the patients receiving cisplatin-containing regimen also displayed more moderate to severe CIA than those receiving non-cisplatin regimen. There were no significant differences were found in

Table 3. Relationships Between Severity of CIA and Potential Associated Factors

Factors	G1	G2	G3/4	χ^2	P-value	Wilcoxon W	P-value
Gender							
Male	53(61.6%)	26(30.2%)	7(8.1%)	0.649*	0.723	5864	0.438
Female	29(31.3%)	19(17.2%)	5(4.6%)				
Age							
≥60	29(58.0%)	19(38.0%)	2(4.0%)	2.718*	0.257	3465.5	0.862
<60	53(52.5%)	26(28.8%)	10(7.7%)				
Regimen							
Cisplatin containing	39(51.3%)	28(36.8%)	9(11.8%)	4.709	0.095	3970	0.033
Non-cisplatin	43(68.3%)	17(27.0%)	3(4.8%)				
Radiotherapy							
Yes	23(50.0%)	18(39.1%)	5(10.9%)	2.310*	0.315	6218	0.134
No	59(63.4%)	27(29.0%)	7(7.5%)				
Decrease of WBC							
Yes	68(57.1%)	41(34.5%)	10(8.4%)	1.635*	0.441	1268	0.364
No	14(70.0%)	4(20.0%)	2(10.0%)				
G3/4 leucopenia							
Yes	27(48.2%)	21(37.5%)	8(14.3%)	6.079*	0.048	5336.5	0.02
No	55(66.3%)	24(28.9%)	4(4.8%)				
Decrease of platelet							
Yes	32(45.1%)	29(40.8%)	10(14.1%)	12.981	0.002	4022	0.000
No	50(73.5%)	16(23.5%)	2(2.9%)				
G3/4 thrombocytopenia							
Yes	6(35.3%)	7(41.2%)	4(23.5%)	7.286*	0.026	8212	0.016
No	76(62.3%)	38(31.1%)	8(6.6%)				

*1 cell have minimum expected count less than 5

gender, age, radiotherapy and decrease of WBC among the groups of different grades of anemia (Table 3).

Discussion

The incidence of anemia in adult cancer patients is determined by numerous factors, particularly the type, stage, duration of malignancy, the type and intensity of treatment. Moreover, CIA as a primary treatment-related anemia has been confirmed a relatively high incidence of mild-to-moderate anemia across the major nonmyeloid tumors treated with chemotherapy (Groopman et al., 1999). The large multinational, prospective survey from the ECAS described the prevalence, incidence, and treatment of anemia in cancer patients (Ludwig et al., 2004), its following analysis about 2,070 non-anemic patients determined several independent risk factors for CIA in cancer patients receiving chemotherapy (Barrett-Lee et al., 2006). Whereas, the estimates of the incidence and prevalence of anemia in cancer patients have varied considerably, probably due to differences in patient populations and study methodologies. In this study, we aimed to analyze the correlation of some potential parameters with CIA in Chinese population with solid cancers.

In our study, 220 cancer patients were included for analysis. Anemia affected the majority of patients with cancer, the prevalence of CIA was 63.2% (139/220) overall, and varied according to the types of cancer, for example, esophageal cancers (86.4%, 19/22) and lung cancers (80.3%, 61/76) represented relatively high incidence of CIA, and gastrointestinal/colorectal cancers (42.9%, 12/28) exhibited low incidence of CIA. Analysis from the ECAS data also found that tumor type was recognized as a factor significantly affected the risk of developing anemia, for example, the patients with lung or gynecologic cancers had greater risk to develop anemia than gastrointestinal /colorectal cancers (Ludwig et al., 2004). In our study, majority of anemic patients presented anemia in their first 3 cycles and all anemic patients during their first 6 cycles. Namely, even in non-CIA patients, the decrease of HB seemed to be a common phenomenon which suggested that the decrease in HB during chemotherapy should be given more attention. These analogous results were reported in large-scale UK population (Barrett-Lee et al., 2000) and ECAS (Ludwig et al., 2004).

In the univariate analysis of our study, male gender, aged 60 years or older, and cisplatin-containing regimen were found to be associated with CIA occurrence. We noticed, in our data, that male, aged, cisplatin-containing regimen were associated with each other, and with lung or esophageal carcinomas. The patients with these factors were susceptible to CIA, the interpretation may be multifactorial, for example, the aged has a poor hemocytogenesis, aged male was reported to be more frequent in lung carcinoma (Owonikoko et al., 2007) and esophageal carcinoma (Bohanes et al., 2012), the patients with lung and esophageal carcinomas were received more cisplatin-containing chemotherapy as standard regimen. Platinum-based therapies were well recognized to cause anemia as reported previously (Groopman et al., 1999; Kosmidis et al., 2005; Spivak et al., 2009). Besides a direct cytotoxic effect of chemotherapeutic agents on bone marrow erythroid progenitors (Rothmann et al., 1981; Hassan et al., 2011), cisplatin-induced nephrotoxicity leaded to a poor response of erythropoietin might be another important mechanism (Miller et al., 1990; Abdel-Razeq, 2004). Moreover, cisplatin-containing chemotherapy was notorious for strong digestive dysfunction, such as anorexia, nausea and vomiting, while decreased food intake was reported as an independent risk factors for both anemia occurrence and the severity of anemia in our previous paper (Gao et al., 2011), thus we believed that decreased food intake caused by chemotherapy might also contribute to CIA.

In our analysis, decrease of WBC or platelet, G3/4 leucopenia or thrombocytopenia were also associated

with CIA occurrence. Furthermore, G3/4 leucopenia and decreased platelet were identified as independent risk factors in multivariate models and were found to be related with the severity of CIA. To our knowledge, few reports described the correlations between anemia and leucopenia or thrombocytopenia after chemotherapy till now. RBC, WBC and platelet are all produced by hematopoietic cells in bone marrow. We presume that the hematopoietic cells have similar inhibitory effect after exposure to myelotoxic chemotherapy agents, because of different lifetime of RBC, WBC and platelet, leucopenia, thrombocytopenia and anemia may appear in different time after chemotherapy. Besides, chemotherapy induced thrombocytopenia might increase the risk of bleeding and loss of RBC, infection associated with chemotherapy-induced neutropenia could also cause the release of some cytokines (e.g., interleukin-1, interferon-γ, tumor necrosis factor) which mediated the inhibition of erythropoiesis (Weiss et al., 2005), these inflammatory cytokines appeared to play a role in anemia in patients with cancers (Aapro et al., 2012). Thus, we reasonably suppose that chemotherapy-induced leucopenia or thrombocytopenia might have potential predictive value for the following CIA. However, it was hard to verify the predictive effect in this retrospective analysis. Additionally, different chemotherapeutic agents may have hobby in different hematopoietic cells, thus, prospective observations and further researches were needed to give a clarification.

In conclusion, our study showed that anemia was observed in majority of Chinese cancer patients receiving chemotherapy. Chemotherapeutic agents, particularly cisplatin-containing, might be important factors to influence on the occurrence of CIA. The occurrences and severity of leucopenia and/or thrombocytopenia were associated with CIA, which suggested that it be worthwhile to pay more attention to the occurrence of CIA in patients with chemotherapy induced leucopenia and/or thrombocytopenia, especially who were receiving cisplatin-containing treatment.

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References

Aapro M, Jelkmann W, Constantinescu SN, Leyland-Jones B (2012). Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. *Br J Cancer*, **106**, 1249-58.

Aapro M, Osterborg A, Gascon P, Ludwig H, Beguin Y (2012). Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. *Ann Oncol*, **23**, 1954-62.

Abdel-Razeq HN (2004). Cancer-related anemia. *Saudi Med J*, **25**, 15-20.

Achariyapota V, Benjapibal M, Chaopotong P (2010). Prevalence and incidence of anemia in Thai patients with gynecologic cancer. *Asian Pac J Cancer Prev*, **11**, 1229-33.

Barrett-Lee PJ, Bailey NP, O'Brien ME, Wager E (2000). Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. *Br J Cancer,* **82**, 93-7.

Barrett-Lee PJ, Ludwig H, Birgegard G, et al (2006). Independent risk factors for anemia in cancer patients receiving chemotherapy: results from the European Cancer Anaemia Survey. *Oncology*, **70**, 34-48.

Bohanes P, Yang D, Chhibar RS, et al (2012). Influence of sex on the survival of patients with esophageal cancer. *J Clin Oncol*, **30**, 2265-72.

Caro JJ, Salas M, Ward A, Goss G (2001). Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*, **91**, 2214-21.

Gao F, Cheng K, Zhao F, et al (2011). Prevalence and characteristics of anemia in patients with solid cancers at diagnosis in southwest China. *Asian Pac J Cancer Prev*, **12**, 2825-8.

Groopman JE, Itri LM (1999). Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst,* **91**, 1616-34.

Hassan BA, Yusoff ZB (2011). Treatment patterns and outcomes in management of solid cancer patients suffering from anemia in Penang hospital. *Asian Pac J Cancer Prev*, **12**, 1573-6.

Hassan BA, Yusoff ZB, Hassali MA, Othman SB (2011). Association and correlation of different chemotherapeutic regimens and doses with onset and severity of anemia among solid cancer patients. *Asian Pac J Cancer Prev*, **12**, 2753-8.

Knight K, Wade S, Balducci L (2004). Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med*, **116**, S11-26.

Kosmidis P, Krzakowski M (2005). Anemia profiles in patients with lung cancer: what have we learned from the European Cancer Anaemia Survey (ECAS)? *Lung Cancer*, **50**, 401-12.

Ludwig H, Van Belle S, Barrett-Lee P, et al (2004). The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer*, **40**, 2293-306.

Mercadante S, Gebbia V, Marrazzo A, Filosto S (2000). Anaemia in cancer: pathophysiology and treatment. *Cancer Treat Rev*, **26**, 303-11.

Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL (1990). Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med*, **322**, 1689-92.

Owonikoko TK, Ragin CC, Belani CP, et al (2007). Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol*, **25**, 5570-7.

Pongsanon K, Benjapibal M, Ruengkhachorn I (2011). Prognostic significance of hemoglobin levels in patients with primary epithelial ovarian carcinoma undergoing platinum-based chemotherapy. *Asian Pac J Cancer Prev*, **12**, 131-6.

Rothmann SA, Weick JK (1981). Cisplatin toxicity for erythroid precursors. *N Engl J Med*, **304**, 360.

Spivak JL, Gascon P, Ludwig H (2009). Anemia management in oncology and hematology. *Oncologist*, **14**, 43-56.

Steensma DP (2008). Is anemia of cancer different from chemotherapy-induced anemia? *J Clin Oncol*, **26**, 1022-4.

Tchekmedyian NS (2002). Anemia in cancer patients: significance, epidemiology, and current therapy. *Oncology (Williston Park)*, **16**, 17-24.

Weiss G, Goodnough LT (2005). Anemia of chronic disease. *N Engl J Med*, **352**, 1011-23.

Wilairat W, Benjapibal M (2012). Presence of anemia and poor prognostic factors in patients with endometrial carcinoma. *Asian Pac J Cancer Prev*, **13**, 3187-90.