RESEARCH COMMUNICATION

Prevalence and Incidence of Anemia in Thai Patients with Gynecologic Cancer

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Abstract

This prospective, single institute, 6-month observational survey aimed to evaluate the prevalence, incidence, frequency, treatment of anemia, and trigger hemoglobin (Hb) level for initiating transfusion in patients with gynecologic malignancy. One hundred and eighty-six consecutive patients with gynecologic malignancy were analyzed between June and December 2009. Hb level data were collected for up to six data points or 6 months of scheduled visits. Tumor type, disease status, cancer treatment and anemia treatment as well as trigger Hb level for starting treatment were evaluated. The mean age of patients was 51 years. Prevalence of anemia at enrollment was 66.1% (123/186), with 36 of 186 patients (19.4%) having moderate to severe anemia (Hb < 10.0 g/dl). The highest prevalence was found among patients with endometrial cancer (72.2%) and ovarian cancer (72%), newly-diagnosed/receiving treatment (70.9%) and those receiving radiotherapy (75%). The incidence of anemia was 85.7% (54/63). Ovarian cancer had the highest association (87%). For disease status and cancer treatment, the incidence was highest in patients with persistent/recurrent disease (95.2%) and those who received radiotherapy (100%). One hundred and seventy-seven of 186 patients (95.2%) were ever anemic during the survey. Anemia was frequently reported in patients with all tumor types (93-100%), persistent/recurrent disease (98.3%) and those who received radiotherapy (100%) and 80.8% of patients who were ever anemic recieved treatment (oral iron, 42.9%; transfusion, 37.3%; and erythropoietic agent, 0.6%). In conclusion, the mean Hb trigger level for initiating transfusion as treatment of anemia was 8.6g/dL. The prevalence, incidence, and frequency of anemia are very high among patients with gynecologic malignancy; especially those with ovarian cancer, persistent/recurrent disease, and those receiving treatment.

Keywords: Anemia - cancer - prevalence - incidence - frequency

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Introduction

Cancer-related anemia results in a variety of symptoms, including dyspnea, headache, exhaustion, weakness, and decline in energy and activity levels. Its cardinal symptom, fatigue, interferes with the daily lives of three-quarters of cancer patients at some time during the course of their disease and its treatment (Vogelzang et al., 1997; Cella, 1998). Its impact on health-related quality of life of cancer patients has been demonstrated by randomized trials and large community based studies (Glaspy et al., 1997; Demetri et al., 1998). Furthermore, anemia has been found to be a poor prognostic factor in patients with cancer (Caro et al., 2001; Van et al., 2003; Alici et al., 2006). The reasons underlying this feature continue to remain unclear. Tumor cells are known to secrete soluble molecules such as interleukin-1, interferon-gamma, and tumor necrosis factor. These tumor-released cytokines induce hemolysis, changes in iron metabolism, endogenous erythropoietin deficiency, and suppression of erythroid progenitor cells. Cancer-related anemia has been regarded as a paraneoplastic phenomenon. In other words, tumors in patients with anemia may have a considerable number of cell clones that are biologically more aggressive than those in patients with higher Hb levels (Mercadante et al., 2000; Bron et al., 2001; Tas et al., 2002; Dicato, 2003; Weiss et al., 2005).

Anemia is a common condition in cancer patients with a prevalence of 30% to 90%, depending on the type of cancer and definition of anemia. It is also difficult to accurately determine the incidence and frequency of anemia from the literature because of its widely varying definitions. According to the European Cancer Anemia Survey (ECAS) and the Australian Cancer Anemia Survey (ACAS), 68% and 57% of patients experienced anemia (generally defined as Hb level below 12 g/dL) at some time during the 6-month follow-up period, respectively. Gynecologic malignancies were among the tumors characterized by a higher prevalence and incidence of anemia during the survey (Ludwig et al., 2004; Seshadri et al., 2005). This study was aimed to identify estimates of anemia prevalence, incidence, frequency, and anemia

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treatment pattern in patients with gynecologic malignancy in Siriraj Hospital.

Materials and Methods

Study design

This study was a prospective, single institute, 6-month observational survey conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. Participants were recruited from consecutive patients attending the Division of Gynecologic Oncology between June and December 2009. Survey data were collected for up to six data points or 6 months of scheduled visits.

Participants

Eligible patients were aged > 18 years, had a diagnosis of gynecologic malignancy, and were scheduled to receive or were currently receiving chemotherapy, radiotherapy or combined modality treatment, or were in follow up. Patients were excluded if they were enrolled in a clinical trial, had diseases which involved Hb status such as hematologic, hepatic or renal diseases. All participants provided written consent after receiving a full explanation of the survey. The study was approved by the Ethics Committee of the institution. All procedures were conducted in accordance with the ethical principles defined in the Declaration of Helsinki. Enrollment data included age, weight, tumor type and stage, disease status, hematologic laboratory values, cancer and anemia treatment within 30 days of survey enrollment. The timing of data collection depended on the cancer treatment being administered. Patients about to receive treatment provided enrollment data before the treatment began. Patients receiving chemotherapy or concomitant chemo-radiotherapy provided enrollment data at the end of each chemotherapy cycle to a maximum of six cycles or 6 months following enrollment. Those receiving radiotherapy provided enrollment data 3-6 weeks after initiation of the treatment, on its completion, and at each subsequent clinical follow-up visit to a maximum of six visits. For patients not receiving chemotherapy or radiotherapy, data were collected at each visit, with a maximum of one per month for the 6-month survey period. Survey completion data were recorded at the last follow-up evaluation at 6 months or after the sixth follow-up evaluation. Follow-up data included weight, disease status, cancer treatment and number of current cycle for patients receiving chemotherapy, hematologic laboratory values (as at enrollment) and anemia treatment.

Definitions

Anemia was defined as Hb<12.0g/dL and was further categorized as mild:11.9-10.0g/dL; moderate:9.9-8.0 g/dL; or severe: <8.0g/dL, based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Prevalence of anemia was defined as the percentage of patients who had anemia at enrolment. Incidence was defined as the percentage of patients who developed anemia during the study among those who were non-anemic at enrolment. Anemia frequency was defined as the percentage of patients who either had anemia at enrolment or developed it during the study.

For disease status, patients were categorized as ''newly diagnosed'' if this was their first occurrence of cancer; these patients were further categorized into newly-diagnosed/not receiving treatment or newly-diagnosed/receiving treatment. Patients were categorized as ''persistent/recurrent'' if their initial tumor had returned or metastasized, or as ''in remission'' if they were being followed after successful cancer treatment. For analysis of anemia frequency by cancer treatment, patients were categorized as: chemotherapy only; radiotherapy only; concomitant chemo-radiotherapy (chemotherapy and radiotherapy administered simultaneously); or follow-up (patient had completed cancer treatment).

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 13.0. Sample characteristics and Hb level were examined with descriptive statistics. Chi's square test was used for proportional data differences.

Results

A total of 186 patients qualified for inclusion in the survey. All patients' data were analyzed. Their characteristics are shown in Table 1.

Prevalence of anemia

Of 186 patients at enrollment, 66.1% (123/186) were anemic. Most patients (46.8%) had mild anemia, with Hb levels between 10.0-11.9 g/dL; moderate anemia was recorded for 15.6% (Hb 8.0-9.9 g/dL), and severe anemia for 3.8% of patients (Hb < 8.0 g/dL). Prevalence varied by tumor type, disease status and treatment type. The prevalence was highest among patients with endometrial cancer (72.2%) and ovarian cancer (72%), among patients with newly-diagnosed/receiving treatment (70.9%), and

Table 1. Demographic Data (n=186)

	n	%
Mean age (range), years	51.7 (20-86)	
Mean body weight (range), kilograms	57.7 (34-98)	
Tumor type		
Ovary	82	44.1
Cervix	57	30.6
Corpus	36	19.4
Gestational trophoblastic neoplasia	4	2.2
Peritoneum	3	1.6
Vagina	2	1.1
Fallopian tube	1	0.5
Vulva	1	0.5
Disease status		
Newly diagnosed, no treatment	32	17.2
Newly diagnosed, with treatment	79	42.5
Persistent or recurrent	59	31.7
Remission	16	8.6
Treatment type		
None	20	10.8
Chemotherapy	133	71.5
Radiotherapy	4	2.2
Concurrent chemoradiation	29	15.6

Table 2. Prevalence, Incidence, and Frequency of Anemia

	Prevalence at enrollment		Incidence during study		Frequency	
	n	%	n	%	n	%
Overall	123/186	66.1	54/63	85.7	177/186	95.2
Hb level						
≥ 12.0 g/dL	63/186	33.9	9/63	14.3	9/186	4.8
10.0-11.9 g/dL	87/186	46.8	22/63	34.9	59/186	31.7
8.0-9.9 g/dL	29/186	15.6	28/63	44.4	92/186	49.5
< 8.0 g/dL	7/186	3.8	4/63	6.3	26/186	14
Tumor type						
Ovary	59/82	72	20/23	87	79/82	96.3
Cervix	33/57	57.9	20/24	83.3	53/57	93
Corpus	26/36	72.2	8/10	80	34/36	94.6
Gestational trophoblastic neoplasia	2/4	50	2/2	100	4/4	100
Peritoneum	1/3	33.3	2/2	100	3/3	100
Vagina	2/2	100	-	-	2/2	100
Fallopian tube	0/1	0	1/1	100	1/1	100
Vulva	0/1	0	1/1	100	1/1	100
Disease status						
Newly diagnosed, no treatment	19/32	59.4	11/13	84.6	30/32	93.7
Newly diagnosed, with treatment	56/79	70.9	19/23	82.6	75/79	94.9
Persistent or recurrent	38/59	64.4	20/21	95.2	58/59	98.3
Remission	10/16	62.5	4/6	66.6	17/19	87.5
Treatment status						
None	13/20	65	5/7	71.4	18/20	90
Chemotherapy	88/133	66.2	41/45	91.1	129/133	97
Radiotherapy	3/4	75	1/1	100	4/4	100
Concurrent chemoradiation	19/29	65.5	7/10	70	26/29	89.7

those receiving radiotherapy (75%) (Table 2).

Incidence of anemia

The incidence of anemia was defined as patients who were not anemic at enrollment but developed anemia during the survey. The overall incidence was 85.7% (54/63); 34.9% of those patients had Hb levels between 10.0-11.9g/dL, 44.4% had Hb levels between 8.0-9.9g/dL, and 6.3% had Hb levels less than 8.0g/dL. Among the three most common gynecologic tumors, patients with ovarian cancer had the highest incidence of anemia (87%), compared with cervical cancer (83.3%) or endometrial cancer (80%). For disease status and cancer treatment, the incidence of anemia was highest in patients with persistent/recurrent disease (95.2%), and those who received radiotherapy (100%) (Table 2).

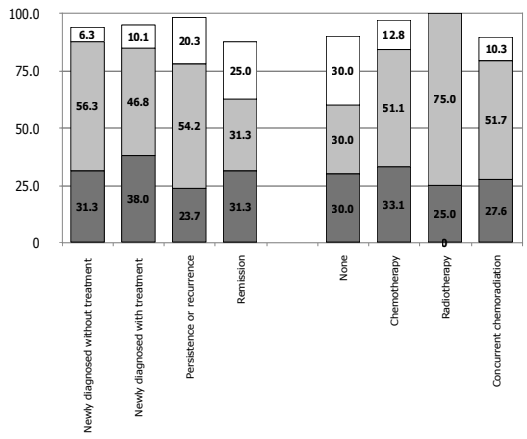

Figure 1. Frequency of Anemia by Disease Status and Treatment Type

Frequency of anemia

The frequency of anemia was defined as patients who had anemia at enrollment or developed anemia during the survey. The overall frequency was 95.2% (177/186). Table 2 shows patients who were ever anemic at enrollment or during the survey by tumor type, disease status and cancer treatment group. Anemia was frequently reported in patients with all tumor types (93-100%). Most of these patients had Hb levels of 8.0-9.9g/dL (49.5%). Anemia was most frequently reported in patients with persistent/recurrent disease (98.3%), and those who received radiotherapy (100%) (Figure 1). There were no statistical differences of anemia frequency among disease status and type of cancer treatment (p value=0.35, and 0.28, respectively).

Treatment of anemia

Of patients who were ever anemic (177), 80.8% received treatment for their anemia. The most frequent treatment was oral iron (42.9%) and more than one-third of patients who were ever anemic (37.3%) received transfusion. Only one patient (0.6%) received erythropoietic agent. The mean Hb trigger level for initiating transfusion as treatment of anemia was 8.6g/dL, ranging from 6.2g/dL to 9.9g/dL. One-third of the patients with normal Hb levels (33.3%) also received anemia treatment with oral iron.

Discussion

Anemia is frequently observed in cancer patients at the time of diagnosis and during treatment. Besides worsening the quality of life (Glaspy et al., 1997; Vogelzang et al., 1997; Cella, 1998; Demetri et al., 1998), anemia itself is associated with shorter survival times for

several cancers (Caro et al., 2001; Van et al., 2003; Alici et al., 2006). The basis for the impact of anemia on the treatment outcome, however, is complex and influenced by many factors. Tumor cells are known to produce and secrete several soluble cytokines (such as interleukin-1, interferon-gamma, and tumor necrosis factor) that may be able to decrease Hb levels by hemolysis, suppression of erythropoiesis, and impairment of erythropoietin response of erythroid medullary precursors. According to this hypothesis, anemia should be regarded as a paraneoplastic syndrome, a phenomenon of the biologic aggressiveness of cancer (Mercadante et al., 2000; Bron et al., 2001; Tas et al., 2002; Dicato, 2003; Weiss et al., 2005). An alternative hypothesis to explain the prognostic role of anemia is that anemia is a major contributing factor to tumor hypoxia, which occurs when the tumor growth exceeds the ability of the local microvasculature to supply oxygen to the tumor cells (Vaupel et al., 2001). Höckel et al., (1996) measured tumor oxygenation using pO2 polarography and found that pO2 levels express radioresistance in the presence of advanced-stage cancer of the uterine cervix. Thus, pO2 was found to be a useful prognostic factor. Previous studies involving patients with cancer have shown that non-anemic tumors are more responsive to adjuvant therapy. Both radiotherapy and chemotherapy were reported to be more effective in well oxygenated than in hypoxic conditions (Dische, 1991; Hockel et al., 1996; Liang, 1996; Eisenhauer et al., 1997; Thews et al., 1998). This could be another reason why anemic cancer patients have poor survival rates. Based on a systemic review of 19 observational studies of patients with cancer, all but one of these studies showed an association between anemia and decreased survival (Knight et al., 2004).

According to the ECAS and ACAS, gynecologic malignancy accounted for 11.5% and 5.5% of the study populations; and the prevalence or percentage of patients who had anemia at enrollment were 49.1% and 65%,respectively (Ludwig et al., 2004; Seshadri et al., 2005). Our present data also show a high prevalence of anemia in patients with gynecologic malignancy (66.1%). Interestingly, the mean baseline Hb levels in our survey are lower than those previously reported. The possible reason underlying this feature is that Thailand is one of the countries reported to have a high prevalence of thalassemia carriers; 20-30% being α-thalassemia, 2-10%, β-thalassemia, and 8-20% Hb E carrier (Fucharoen et al., 1988; Panich et al., 1992). In the European and Australian surveys, patients with gynecologic malignancy had a high risk of developing anemia with the incidences of 55% and 64.6%, respectively (Ludwig et al., 2004, Seshadri et al., 2005). Our data are consistent with those results suggesting a high percentage of patients who developed anemia during the study. The incidence of anemia in our study (85.7%) is somewhat higher than those previously reported. Gynecologic malignancy are often treated with platinum-based chemotherapy, either cisplatin or carboplatin. Low baseline Hb levels, platinum-based chemotherapy and gynecologic malignancy have been shown to be the independent predictors of developing anemia in cancer patients (Barrett-Lee et al., 2005). Our study shows that anemia is common among patients with gynecologic malignancy with 95.2% of patients either having anemia at enrollment or developing it during the follow-up and 63.5% either having or developing moderate to severe anemia. Patients who received radiotherapy (100%) as well as chemotherapy (97%) were more likely to have anemia than those who received concomitant radiotherapy (89.7%) or those in the follow-up category not receiving cancer treatment (90%).

Previous studies involving patients with cancer have shown the association between anemia and worsening the quality of life, poor response to treatment, and decreased survival rates. Selecting the optimal Hb level for intervention with anemia treatment may become essential for improving quality of life and possibly other outcomes for cancer patients (Barrett-Lee et al., 2005). The American Society of Hematology/American Society of Clinical Oncology and the European Organization for Research and Treatment of Cancer have recommended the guidelines for anemia treatment (Bokemeyer et al., 2007; Aapro et al., 2008; Rizzo et al., 2008). Surprisingly, approximately eighty percent (143/174) of ever anemic cancer patients in our study received treatment of anemia. This figure is much higher than those previously reported by the European (42.7%) and Australian Survey (48%) (Ludwig et al., 2004, Seshadri et al., 2005). Oral iron accounted for a majority of anemia treatment (42.9%) followed by blood transfusion (37.3%). In our Division, oral iron is routinely prescribed to all patients receiving chemotherapy. The mean Hb trigger level for initiating transfusion was 8.6 g/dL which is lower than those reported previously (9.7 g/dL). It seems that guidelines have not been followed in our patients and initiation of anemia treatment depends on the discretion of the physicians. Only one patient in the survey (0.6%) received erythropoietic agent. The low usage of these agents in our patients may be because they are not currently reimbursed by the Universal Coverage Health Care Scheme in Thailand and the price is costly.

Our survey has revealed a high prevalence, incidence and frequency of anemia in patients with gynecologic malignancy. The limitation of this study is selection bias, as only selected patients from one institute were included. So, our participants may not represent the population with gynecologic malignancy in the community. However, concerning that anemia has the adverse impact on both quality of life and treatment outcome, physicians taking care of patients with gynecologic malignancy should take this into consideration.

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