Prevalence, Incidence and Management of Anemia in Cancer Patients Treated in the Radiation Oncology Division, Siriraj Hospital

Pawinee Mahasittiwat, M.D.*, Pittayapoom Pataranutraporn, M.D.*, Nantakan Ieumwananonthachai, M.D.*, Pittaya Dankulchai, M.D.*, Yaowalak Chansilpa, M.D.*, Supatra Sangruchi, M.D.*, Vutisiri Veerasarn, M.D.*, Nan Suntornpong, M.D.*, Kullathorn Thephamongkhol, M.D.*, Janjira Petsuksiri, M.D.*, Suthipol Udompunturak, M.Sc.**

**Department of Radiology, Office for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: This study was designed to find the prevalence of anemia in cancer patients before radiotherapy and the incidence of anemia during radiotherapy treatment. The study also planned to identify factors that affect the incidence and prevalence of anemia and the management of anemia in the Division of Radiation Oncology, Siriraj Hospital.

Methods: This study is designed prospectively to collect hemoglobin level and factors that might cause anemia in patients whom were treated with radiotherapy at Siriraj Hospital during April - June 2006. The eligible criteria were patients age > 18 years old, had a pathology confirmed to be malignancy, and had never been treated with radiotherapy before. Patients were excluded if they were not treated with radiotherapy, had skin/central nervous system or hematologic malignancies. In this trial, anemia was defined as Hb level <12 g/dl for both genders.

Results: It was found that the prevalence of anemia within 30 days before starting radiotherapy was 54.4% and the incidence of anemia during radiotherapy was 34.3%. The frequency of anemia, defined as the number of patients in the study in whom Hb <12.0 g/dL were found at least once either at enrollment or during the survey, was 66%. Previous chemotherapy was the main predicting factor for anemia before radiotherapy. Concurrent chemo-radiotherapy patients developed a higher incidence of anemia during the survey than patients with radiotherapy alone. The incidence of anemia was highest in gynecologic malignancy patients. Only 25/112 (22.3%) of anemic patients at initial evaluation received treatment for anemia. Most of the patients were treated with a blood transfusion and none was treated with erythropoietin. Our mean trigger hemoglobin level for treatment of anemia was 9.3 g/dl.

Conclusion: Anemia is common in the patients who are treated with radiotherapy in our institute with the prevalence of anemia before starting radiotherapy as high as 54.4% especially in patients previously treated with chemotharapy. One-thirds of patients developed anemia during radiotherapy, with a higher incidence in gynecologic malignancy patients and patients who receive combined chemo-radiotherapy. The total frequency of anemia in patients treated in the Division of Radiation Oncology, Siriraj Hospital was as high as 66% before and during radiotherapy.

Keywords: Anemia, cancer, radiotherapy

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Anemia is the most common hematologic abnormality associated with cancer, occurring in approximately 50% of cancer patients during the course of their illness.[1,2] It results can be either directly from the malignancy or as a consequence of treatment. Anemia is an important aspect in cancer treatment. Anemia in cancer patients causes many symptoms including fatigue, drowsiness, depression, shortness of breath, tachycardia and dizziness. Of these symptoms, fatigue is the most common and has the most intense effect on patient quality of life (QoL).[3-6] Based on cumulative survival data from 60 papers stratified by Hb or anemia, Caro et al. found anemia in cancer is related to increased mortality in diseases such as lung, prostate, Head and neck cancer and lymphoma[7]. Furthermore, many studies reported the impact of anemia on results of treatment and prognosis of head and neck, and cervical cancer patients[8-11]. Because the patient populations and study methodologies are probably

Correspondence to: Pawinee Mahasittiwat
E-mail: nee_rt@yahoo.com

different, the incidence and prevalence of anemia in cancer patients have considerable diversity. From the European Cancer Anemia Survey (ECAS) study,[12] the prevalence of anemia with hemoglobin level < 12 g/dl at enrollment was 39.3%. The Australian Cancer Anemia Survey (ACAS) study[13] similarly concluded that prevalence of anemia at their enrollment was 35%, with 78% of the anemic patients having mild anemia (hemoglobin (Hb) 10.0–11.9 g/L). Patients who received radiotherapy combined with chemotherapy either sequentially or concomitantly were more likely to have anemia (73%) than those receiving chemotherapy alone (58%) (P = 0.004). This leads to the question whether the patients who received radiotherapy are more anemic at the beginning or patients have developed anemia from radiation treatment.

The treatments of anemia are varied both in the ways of the treatment and the trigger hemoglobin level to start the treatment. European and Australian data showed that the treatments were varied among doctors' decision, however similar trigger hemoglobin level were reported: ECAS; 9.7 g/dl and ACAS; 9.5 g/dl.

Data of Thai cancer patients from Voravud N, et al showed that the prevalence of patients having a hemoglobin level < 12 g/dl was 53%[14], which is higher than the European and Australian data. The Thai Cancer Anemia Survey in Siriraj Hospital was initiated to document the prevalence of anemia before radiotherapy, incidence of anemic cancer patients who are treated with radiotherapy and to study the management of anemia in our institute.

MATERIALS AND METHODS

This study was designed as a prospective study to survey the hemoglobin level and management of anemia in patients who attend the radiation oncology clinic at Siriraj Hospital. All of the patients planned for radiotherapy in the clinic from April 1st 2006 were screened. The patients were eligible if they were at least 18 years of age; had pathology which confirmed malignancy; and would be treated with radiation treatment. The patients were excluded if they had skin, central nervous system tumor, or hematologic malignancies. (Our unpublished retrospective data showed that skin and CNS tumor patients had very low incidence of anemia.)

The initial hemoglobin was defined as hemoglobin level within 30 days before starting radiotherapy. CBC was scheduled for initial evaluation and then followed up every week for patients with initial Hb< 12 g/dl and every 2 weeks for patients with initial Hb> 12 g/dl.

The collected data at enrollment and during the treatment were: Age, sex, Karnofsky Performance Status Scale (KPS), underlying medical diseases, cancer site, aim of treatment (curative vs. palliative), previous treatment (surgery, chemotherapy), cancer treatment during radiotherapy period (RT alone or concurrent chemo-radiation), CBC for initial Hb and subsequent Hb during radiotherapy.

Anemia was defined as Hb level less than 12 g/dl for both genders. The frequency of anemia was determined by the number of patients in the analysis population in whom low hemoglobin values (Hb < 12.0 g/dl) were found at least once at enrollment or during treatment ("ever anemic"). The incidence (new case) of anemia was defined as the percentage of patients who were not anemic at enrollment but developed anemia during the survey.

The treatment of anemia for each patient was determined by the individual's physician, the treatment and the trigger hemoglobin level were collected.

The sample size was calculated using a two-sided test, with expected proportion of anemia to be 62% according to our unpublished retrospective data and the distance from this proportion to limit was +7%. With a 95% confidence interval, the sample size is 184 cases.

When we estimate 10% of loss from follow-up, then the final sample size would be 204 patients.

RESULTS

Two hundreds sixty-seven new patients who were treated with radiation therapy in Siriraj Hospital during April to June 2006 were entered into the study. Sixty one patients were excluded due to age < 18 years old (6), primary skin (7), CNS (4), hematologic malignancy (19), incomplete blood examination (15), prior radiotherapy (4), pregnancy (1) and no definite pathology confirmed (5). The patients who met the inclusion/exclusion criteria were totally 206 cases with the characteristics shown in Table 1.

TABLE 1. Patient characteristics.

Patient Characteristics	No. of patients (%)
Demographic data	
Age (years)	
Range	18-89
Mean	53.3
Median	52
Sex	
Male	66 (32%)
Female	140 (68%)
Residence	
Bangkok	74 (35.9%)
Others	132 (64.1%)
Disease sites	
Head and neck	45 (21.8%)
Thorax	19 (9.2%)
Abdomen	14 (6.8%)
Gynecology	63 (30.6%)
Cervix	48 (23.3%)
GU tract	3 (1.5%)
Musculo-skeleton	3 (1.5%)
Breast	54 (26.2%)
Opthalmic site	0 (0%)
Others	5 (2.4%)
Aim of treatment	
Curative	145 (70.4%)
- Concurrent Chemo-RT	65 (31.6%)
- RT alone	80 (38.8%)
Palliative	61 (29.6%)
Previous treatment	
Surgery alone	65 (31.6%)
Surgery + Chemotherapy	73 (35.4%)
Chemotherapy alone	8 (3.9%)
No treatment	60 (29.1%)
KPS	
80-100	170 (82.5%)
50-70	26 (12.6%)
0-40	0 (0%)
Unknown	10 (4.9%)

Prevalence of anemia at initial evaluation

The prevalence of anemia at the time of enrollment was 54.4% (112/206 patients). Seventy-three percents of patients (82/112) had a hemoglobin level in the range of 10 to 11.9 g/dl and 27% (30/112 patients) of patients had a hemoglobin level less than 10 g/dl.

The prevalence of anemia at initial evaluation within 30 days before starting the radiotherapy classified by the site of disease was presented in Table 2. The most common site was cervical cancer with the prevalence of anemia of 66.7%.

No significant difference of patient characteristics: Age, sex, KPS, underlying medical diseases between the anemic group and the non-anemic group were demonstrated. There was also no significant difference of the prevalence of anemia among the previously treated group and the untreated group (p-value = 0.24, 0.9, 0.54 and RR = 0.79, 1.04, 1.32 respectively for patients previously treated with surgery alone, surgery plus chemotherapy, and chemotherapy alone groups compared to the no previous treatment group) as shown in Table 3.

Incidence of anemia during radiotherapy

The incidence of anemia was calculated from the non-anemic group at initial evaluation (n=94 patients) who developed anemia during the survey. Only 67 patients (71%) had periodic complete blood count during radiotherapy as planned. Thirty four percents of these patients (23/67) developed anemia with a Hb level < 12 g/dl, 7.5% had a Hb level < 10 g/dl and 26.9% had a Hb level of 10-11.9 g/dl as shown in Table 4. The groups of patients, classified by region of cancer, who mostly developed anemia during treatment were gynecologic malignancy (10/19 patients, 52.6%) and head and neck cancer (9/18 patients, 50%) patients.

Gynecologic, head and neck cancer and lung cancers were diseases that have the role of concurrent chemo-radiotherpay. The data showed that patients treated with concurrent chemo-radiotherapy in these disease sites were more likely to develop anemia during the treatment (15/23, 65.2%) when compared with patients who were treated with radiotherapy alone (5/18, 27.8%), as shown in Table 5.

Frequency of anemia

The frequency of anemia (“ever anemic”) was determined by the number of patients in the analysis population in whom low hemoglobin values <12.0 g/dL were found at least once either at enrollment or during the survey. Table 6 showed the frequency of anemia from the survey, 136 in 206 patients (66%) were found to have a hemoglobin level less than 12 g/dl while 49% had a hemoglobin level 10-11.9 g/dl and 17% had a hemoglobin level less than 10 g/dl. Most patients with a hemoglobin level less than 12 g/dl were gynecologic malignancy and head and neck cancer patients. However the complete blood counts during the treatment were investigated completely as planned in only 74.3% of patients, so the real number of frequency of anemia might be higher.

Treatment of anemia

Only 25 of 112 (22.3%) anemic patients at initial evaluation received treatment for anemia. The treatments were composed of blood transfusion and oral iron supplement as shown in Table 7. The treatment for anemia varied according to the physician's judgment. The mean trigger Hb level of treatment for initial evaluation was 9.3 g/dl (5.8-11.5 g/dl). Twenty-three of 101 anemic events were treated during radiotherapy. A few patients were treated with folic acid supplement as shown in Table 7. None of our patients received erythropoietin for treatment of anemia.

TABLE 2. Prevalence of anemia at initial evaluation within 30 days before radiotherapy classified by site of cancer.

Site of disease	Total no.	Total anemic		Anemic patients		Non anemic
				Hb < 10 g/dL	Hb 10-11.9 g/dL	Hb ≥ 12 g/dL
		No.	%	No.	No.	No.
Head and neck	45	20	44.4	7	13	25
Lung	19	9	47.4	4	5	10
Breast	54	32	59.3	6	26	22
GI	14	7	50	2	5	7
GYN	63	39	61.9	11	28	24
Cervix	48	32	66.7	9	23	16
GU	3	2	66.6	0	2	1
Musculo-skeleton	3	0	0	0	0	3
Other	5	3	60	0	3	2
Total	206	112	54.4	30	82	94

TABLE 3. Prevalence of anemia at initial evaluation classified by previous treatment (N=206 patients).

Previous treatment	Hb < 12 g/dL	Hb > 12 g/dL	p value	Relative risk	95%CI
Surgery alone	29	36	0.24	0.79	0.56-1.12
Surgery + Chemotherapy	43	30	0.90	1.04	0.78-1.39
Chemotherapy alone	6	2	0.54	1.32	0.84-2.09
No treatment	34	26			

DISCUSSION

Definitions of anemia differ slightly from various references, the World Health Organization defines anemia as a Hb level < 10.9 g/dl[15] while the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute (NCI)[16] define anemia as a Hb level < 12.0 g/dL. We used a Hb < 12 g/dL as anemia in this study to be able to compare our results with European, Australian and previous Thai anemic studies.[12-14]

Anemia may be the result of the malignancy itself, cancer treatment, blood losses, nutritional deficiencies, hemolysis, endocrine disorders, or an inflammatory cytokines associated with chronic diseases. As mentioned before the incidence and prevalence of anemia in cancer patients diverse considerably from each report which may be from the diversity of

TABLE 4. Incidence of anemia developed during the course of radiotherapy.

Site of disease	No. of Pts evaluated	Total incidence No.	Anemic patients %	Hb < 10 g/dL No.	Hb 10-11.9 g/dL No.	Non anemic Hb ≥ 12 g/dL No.
Head and neck	18	9	50	3	6	9
Lung	4	1	25	0	1	3
Breast	15	2	13.3	0	2	13
GI	6	0	0	0	0	6
GYN	19	10	52.6	2	8	9
Cervix	11	6	54.5	1	5	5
GU	1	0	0	0	0	1
Musculo-skeleton	3	0	0	0	0	3
Other	1	1	100	0	1	0
Total	67	23	34.3	5	18	44

TABLE 5. Incidence of anemia developed during the course of radiotherapy in patients who treated with concurrent chemoradiotherapy and radiotherapy groups.

Site of disease	No. of Pts evaluated	Concurrent chemoradiotherapy No.	Concurrent chemoradiotherapy Anemic	Radiotherapy alone No.	Radiotherapy alone Anemic
Head and neck	18	8	6	10	3
Lung	4	1	1	3	0
GYN	19	14	8	5	2
Cervix	11	9	5	2	1
Total	41	23	15	18	5

TABLE 6. Frequency of anemia in the Division of Radiation Oncology, Siriraj Hospital, classified by disease site.

Site of disease	Total Patients No.	Total Anemic No.	Anemic patients %	Hb < 10 g/dL No.	Hb 10-11.9 g/dL No.	Non anemic Hb ≥ 12 g/dL No.
Head and neck	45	28	62.2	8	20	17
Lung	19	11	57	5	6	8
Breast	54	34	63	6	28	20
GI	14	7	50	2	5	7
GYN	63	50	79.4	14	36	13
Cervix	48	41	85.4	11	30	7
GU	3	2	66.6	0	2	1
Musculo-skeleton	3	0	0	0	0	3
Other	5	4	80	0	4	1
Total	206	136	66	35	101	70

TABLE 7. Treatment of anemia at initial evaluation and during radiotherapy.

Anemia at Initial evaluation (112)	No. of patients receiving treatment	Bl	Bl+ Iron	Bl+ Iron + folic	Iron	Folic	Iron+ folic
Hb < 10 g/dL (30)	20	17	3	0	0	0	0
Hb 10-11.9 g/dL (82)	5	2	3	0	0	0	0
Anemic events at during radiotherapy (101)	**No. of events receiving treatment**	**Bl**	**Bl+ Iron**	**Bl+ Iron + folic**	**Iron**	**Folic**	**Iron+ folic**
Hb < 10 g/dL (36)	19	12	1	1	3	1	1
Hb 10-11.9 g/dL (65)	4	0	1	0	1	1	1

Bl = blood transfusion, Iron = oral iron supplement, Folic = folic acid supplement

the patient populations and study methodologies. Our study found that the prevalence of anemia at initial evaluation was 54.4%. It was higher than the prevalence from ECAS (39.3%)[12] and ACAS (35%)[13] but consistent with Thai data reported by Voravud N[14]. This might represent the higher incidence of anemia in Thai cancer patients population compared to European and Australian cancer patients. Also the study population in our study concentrated on the patients who have never received radiotherapy and are planned for radiation treatment while other studies based on any cancer patients with any treatments.

The prevalence at enrollment from ACAS in patients who received combination therapy (chemotherapy and radiotherapy), concomitant therapy and radiotherapy were 44%, 31% and 50%, respectively. According to the study of ECAS in the subset of 1,567 patients who received radiotherapy (24% were receiving radiotherapy at enrollment, while 76% went on to receive radiotherapy during the survey period), they found that at enrollment, 23% of these patients were anemic, with the highest rates of anemia occurring in patients with gynecologic cancer, gastrointestinal or colorectal cancer, and lung cancer[17]. We found similar results that the gynecologic cancer especially cervical cancer patients ranked the highest prevalence rate of anemia at the initial evaluation. Our GU patients had also high prevalence of anemia but the number was too small with only 3 patients from the survey. GI and lung cancer showed 50% and 47.4% anemic patients which the incidence is higher than the European study. Breast cancer in contrast also had a high prevalence of anemia (59.3%) in our study that might be because most of the patients had just finished chemotherapy before coming for radiation treatment.

Mercadante S, et al. reported that between 30 and 50% of cancer patients develop anemia at some point in time[18] while the incidence in pediatric

and elderly patients appears to be even higher.[19-20] Olmi P. showed that the severity of anemia was directly correlated with worse performance status.[17] The prevalence of anemia seemed to higher in patients who treated with combined treatment especially in patients who received chemotherapy. In our study which excluded pediatric patients, there was no significantly different prevalence of anemia in older patients and patients with poor performance status detected between the anemic patients group and the non-anemic group. However previous treatment seems to relate with the prevalence of anemia at our initial evaluation with previous chemotherapy as the most significant treatment factor that increases the relative risk to 1.32.

Our study demonstrated that the incidence of anemia after treatment in non-anemic patients was 34% while 20% of radiotherapy-treated patients in ECAS who were not anemic at the time of enrollment became anemic during radiotherapy.[21] This might be the results of our large populations of cervical and head & neck cancer patients who received concurrent chemoradiotherapy. Harrison L, et al. analyzed retrospective data in 574 cancer patients undergoing radiotherapy at Beth Israel Medical Center and found that 41% of the patients were anemic (Hb < 12 g/dL) at initial evaluation; by the end of radiotherapy, this percentage increased to 54%. Anemia was most prevalent in patients with uterine cervical cancer (75%), increasing to 79% by the end of radiation therapy.[22] In our study the prevalence of anemia for cervical cancer before start of radiotherapy was 66.7% and increased to 85.4% at the end of treatment.

Twenty five of the anemic patients (22.3%) in this study received treatment at initial evaluation which was less than the patients from the ECAS and ACAS studies. The retrospective study of F-ACT (French Anemia Cancer Treatment) demonstrated that 44% of 2,782 patients treated for solid tumors and/or malignant hematological diseases had a level of Hb < 11 g/dL. Approximately 2/3 of the anemic patients received treatment by erythropoiesis stimulating agent (ESA) and approximately 17% of them did not receive any specific treatment for this anemia. The median level of Hb at the introduction of the ESA was 10 g/dL[23]. Interestingly, most patients in our study received a blood transfusion for the treatment of anemia and none received erythropoietin. The different ways of treatment of anemia were due to physician's judgment, different diseases, reimbursement and the various financial status of the patients. Also in this study, the patients came for radiotherapy which requires a higher Hb level for the radiosentizing effect, and in this case the ways to rapidly increase Hb level is preferred. However, the mean hemoglobin trigger in our study (9.3 g/dl) was similar with data from two studies (ECAS; 9.7 g/dl and ACAS; 9.5 g/dl).

For the limitations of this study, even though this is a prospective study we still found 23.8% of the patients did not complete monitoring of the complete blood count as planned, and this percentage was lower than that in the ACAS study (44.7%) but higher than that of the ECAS study (8.6%).

CONCLUSION

In conclusion, anemia is common in the patients who received radiotherapy in Siriraj Hospital with frequency of as high as 66% before and during radiotherapy. It is important to detect and treat anemia early in order to improve the results of treatment, especially in gynecologic malignancy, head and neck cancer patients and patients who receive combined chemo-radiotherapy.

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