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STUDY OF ANEMIA PROFILE IN PATIENTS WITH SOLID MALIGNANCIES

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ABSTACT: INTRODUCTION: Anemia is a frequent debilitating problem and complication of cancer, both at the time of diagnosis and during treatment. It negatively affects the quality of life of cancer patients. Despite being more common in hematologic malignancies, anemia is frequently seen in solid tumors. Most studies show the relationship of anemia in patients with solid tumors or leukemias after the start of chemotherapy. My study aims to find the prevalence and type of anemia in patients diagnosed with malignant solid tumors prior to the start of chemotherapy. **MATERIALS AND METHODS:** All the patients that came with treatment naive solid malignancies filling the study criteria were examined and detailed clinical history was taken and thorough physical examination was done. The anemia profile was evaluated by using the following tests: Complete Blood Count with peripheral blood smear, serum iron, TIBC, serum ferritin, reticulocyte count, vitamin B12, Serum LDH. **RESULTS:** The mean age of the cases of solid malignancies in our study was found to be 60 years and out of the 90 cases, 61 were females. The most commonly noted solid malignancies in our study were gynecological (36.6%) out of which the highest number of cases were of the uterus (25.6%), ovaries (9.9%) and cervix (1.1%). The prevalence of anemia increased from 35.4% in stage I – II to 45.2% in stage III and 53.6% in stage IV patients. Out of the 82 patients with anemia, 73 patients (89%) had microcytic hypochromic anemia. Rest of the patients had anemia of normocytic normochromic type (2.4%). In our study, majority of gynecological tumor patients with anemia had a history of bleeding (93.3%) which was a contributing factor for the higher anemia prevalence observed among these tumor types. **CONCLUSION:** The present study has shown that the main etiology of anemia in Indian cancer patients is iron deficiency. It is a widespread and serious problem especially among gynecological, colorectal, lung and breast cancer patients. Its early evaluation and management could reduce the incidence of treatment-related anemia in cancer patients. Measures directed towards characterization and treatment of anemia should be incorporated as an integral part of cancer management protocols. Patients with anemia should be closely monitored, and a vigilant management strategy should be implemented to reduce the risk of morbidity associated with anemia.

KEY WORDS: anemia, leukemia, malignancy, chemotherapy, ferritin, Reticulocyte count

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

INTRODUCTION

Anemia is defined as a hemoglobin level less than 13 g/dl in men and less than 12 g/dl in non-pregnant women.[1] It is a frequent debilitating problem and complication of cancer, both at the time of diagnosis and during treatment. It negatively affects the quality of life of cancer patients. Despite being more common in hematologic malignancies, anemia is frequently seen in solid tumors.[2] The origin of anemia in cancer patients is often multifactorial with three main responsible mechanisms: blood loss, increased destruction of red blood cells (RBCs) and decreased production of functional RBCs.[3] Other conditions may worsen these mechanisms creating a vicious circle: renal failure, nutritional deficiencies (especially folate and B12 deficiency), coagulopathies and severe inflammatory processes.[4] The cancer itself may act directly on the bone marrow by invasion and metastasis leading to suppression of erythropoiesis or indirectly through cytokine release leading to iron sequestration and dyserythropoiesis.[3,4] Furthermore, cytotoxic chemotherapy may worsen the anemia either by impairing erythropoiesis or by its nephrotoxic effect added to the myelotoxicity that accumulates over the course of the treatment. Among chemotherapeutic agents, platinum based regimen and taxanes were most commonly associated with grade III-IV anemias.[5] Moreover, cytokine overproduction alters the iron availability for erythropoiesis leading to an entity called functional iron deficiency (FID). FID is defined as serum transferrin saturation less than 20 % or ferritin less than 100 ng/mL.[6] Although the reserves are satisfactory, the presence of an inflammatory process causes the iron to become 'trapped' in macrophages and enterocytes, limiting its availability to the bone marrow, triggering anemia. As expected, FID is the predominant mechanism of iron deficiency associated with cancer. The prevalence of FID in oncology patients ranges from 29 to 46%, and of iron deficiency associated to anemia ranges from 7 to 42%.[7,12] The abnormal reduction in RBCs and the resultant decrease in hemoglobin leads to reduction in the oxygen carrying capacity of the blood. In turn, it leads to weakness, pallor, dyspnea, and most commonly easy fatiguability.[10] Anemia can compromise the delivery of sufficient amounts of oxygen to all cells, including tumor cells. This hypoxic condition can worsen the results of radiotherapy and chemotherapy, because low tissue oxygenation is associated with a reduced sensitivity of tumors to radiation and some forms of chemotherapy, contributing to the progression of cancer and reduction in survival. Furthermore, there is abundant evidence suggesting that hemoglobin levels of less than 12 g/dl result in worse quality of life and functional status for cancer patients when compared with higher levels.[13] Anemia appears to have a direct effect on health-related quality of life across the spectrum of many disease conditions. The presence of anemia has been linked to frailty, functional impairment, mobility impairment, and falls in older persons. This is caused by the increase of incidence and prevalence of anemia with aging, gender related changes in sex hormones, and the accumulation of comorbid conditions.[14] Most studies show the relationship of anemia in patients with solid tumors or leukemias after the start of chemotherapy, due to the above mentioned mechanisms. My study aims to find the prevalence and type of anemia in patients diagnosed with malignant solid tumors prior to the start of chemotherapy.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

AIM AND OBJECTIVES

AIM:

1) To evaluate the anemia profile and to study the nature and severity of anemia in patients diagnosed with solid malignancies.

OBJECTIVES:

1) To study the prevalence of anemia in patients diagnosed with solid malignancies.
2) To study the type and severity of anemia in patients diagnosed with solid tumors by use of blood investigations.

MATERIALS AND METHODS

This was a hospital based observational, cross-sectional study on evaluating the anemia profile in patients with solid malignancies, studying the nature and severity of anemia, and also to assess the quality of life of these patients. It was performed in patients that were admitted to, SMS Multispeciality Hospital, DR M K Shah Medical College and Research Center Medical College, Ahmedabad, Gujarat, India from January 2019. Enrollment of participants was done after approval from the Institute Research Review Committee and Institute Ethics Committee.

All the patients that came with treatment naive solid malignancies filling the study criteria were examined and detailed clinical history was taken and thorough physical examination was done.

The anemia profile was evaluated using the following tests:

- Complete Blood Count (CBC)
- Peripheral blood film (PBF)
- Serum Iron
- Total Iron Binding Capacity (TIBC)
- Serum Ferritin
- Reticulocyte count
- Serum Lactose Dehydrogenase (LDH)
- Serum Vitamin B12

INCLUSION CRITERIA:

- Patients with histopathological or radiologically confirmed solid malignancy have been included in the study.
- Patients who provided written informed consent.

EXCLUSION CRITERIA:

- Patients with primary haematological malignancies.
- Patients on chemotherapy or those who underwent surgery for malignancy.
- Patients with previous history of anemia, or repeated blood transfusions.

ETHICAL CLEARANCE

Ethical clearance was obtained from Institutional Ethical Committee. Informed Consent was taken from patient and/or patient's relatives. Confidentiality of data was maintained at each stage of study. Option to exit study was kept open at all times.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

RESULTS AND OBSERVATIONS

Table 1: Sex distribution in different age groups

AGE	NO. OF PATIENTS	MALES	PERCENTAGE OF MALES	FEMALES	PERCENTAGE OF FEMALES
<20	2	0	0	2	100
21-30	17	4	23.6	13	76.4
31-40	14	2	14.2	12	85.8
41-50	20	6	30	14	70
51-60	22	6	27.2	16	72.8
61-70	7	4	57.1	3	42.9
71-80	7	6	85.8	1	14.2
81-90	1	1	100	0	0

Table 2: Etiology of solid malignancies

ETIOLOGY	NO. OF PATIENTS	PERCENTAGE
Ca. Uterus	23	25.6
Ca. Breast	13	14.5
Ca. Colon	11	12.2
Ca. Ovary	9	9.9
Ca. Gall Bladder	7	7.8
Ca. Rectum	7	7.8
Hepatocellular Ca.	5	5.6
Ca. Thyroid	4	4.5

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

Renal Cell Ca.	2	2.2
Fibrosarcoma	2	2.2
Ca. Stomach	1	1.1
Ca. Larynx	1	1.1
Ca. Lung	1	1.1
Ca. Prostate	1	1.1
Ca. Cervix	1	1.1
Adrenocortical Ca.	1	1.1
Neuroblastoma	1	1.1
TOTAL	90	100

Table 3: Anemia prevalence

HEMOGLOBIN	NO. OF PATIENTS	PERCENTAGE
2-4	2	2.2
4-6	9	9.9
6-8	23	25.6
8-10	28	31.1
10-12	20	22.3
12-14	6	6.7
>14	2	2.2
TOTAL	90	100

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

Table 4: Sex distribution of anemia

HEMOGLOBIN	NO. OF PATIENTS	MALES	PERCENTAGE OF MALES	FEMALES	PERCENTAGE OF FEMALES
2-4	2	1	50	1	50
4-6	9	4	44.4	5	55.5
6-8	23	10	43.4	13	56.5
8-10	28	11	39.2	17	60.7
10-12	20	1	5	19	95
12-14	6	1	16.6	5	83.3
>14	2	1	50	1	50

Table 5: Intensity of anemia

GRADE	HEMOGLOBIN	TOTAL NO. OF PATIENTS	MALES	PERCENTAGE OF MALES	FEMALES	PERCENTAGE OF FEMALES
0 – Normal	>12	8	2	25	6	75
1 – Mild	10-12	20	1	5	19	95
2 – Moderate	8-10	28	11	39.2	17	60.7
3 – Severe	6.5-8	19	8	42.1	11	57.8
4 – Life Threatening	<6.5	15	7	46.6	8	53.3

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

Table 6: Etiology of anemia

DIAGNOSIS	NO. OF PATIENTS	PERCENTAGE
Iron Deficiency	68	83
Serum B12 Vitamin Deficiency	7	8.5
Chronic Disease	5	6.1
Other Causes	2	2.4
TOTAL	82	100

Table 7: Association of blood loss with solid malignancies

HISTORY OF BLEEDING	NO. OF PATIENTS	PERCENTAGE
Yes	47	51.7
No	43	47.3
TOTAL	90	100

Table 8: Association of blood loss with anemia

GRADE0	%	GRADE1	%	GRADE2	%	GRADE3	%	GRADE4	%
4	8.5	9	19.1	19	40.4	9	19.1	6	12.9

Table 9: Association of fatigue with severity of anemia

FATIGUE	SEVERITY OF ANEMIA					TOTAL
	0	1	2	3	4	
0-50	4	12	11	8	8	43
50-100	4	8	17	11	7	47

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

DISCUSSION

The mean age of the cases of solid malignancies in our study was found to be 60 years and out of the 90 cases, 61 were females (67.7%). Toledano A et al in their study observed median age of patients was 64 years (21-90 years). Ludwig H et al. also observed mean age of patients as 65.0 (22.5–96.8), with male preponderance, 59% of their subjects being males.[11,12] Risk of developing cancer increases with age, more than a third (36%) of all cancers is diagnosed in people aged 75 years or over. Over half (53%) of all cancers occur in people aged 50-74 years.[13] A female preponderance was found in our study, females being more anemic than males, because of the fact that majority of the cases noted were from gynecology and 93.3% of these patients had a history of bleeding. This was also observed by other authors such as Gao F et al., Hassan FM et al. and Verbeke N et al. in their studies in China, Sudan and Belgium respectively.[14.15,16] According to our study, the overall prevalence of anemia across different solid malignancies was 91%, which was much higher than the studies conducted in China (18.98%), Europe (39.3%), Australia (35%), USA (41%), Thailand (54.4%)[2] and Belgium (55.7%).[14,16,17.18,19,20,] A higher prevalence in our study is because of difference in definition of anemia, study population and survey period. The most commonly noted solid malignancies in our study were gynecological (36.6%) out of which the highest number of cases were of the uterus (25.6%), ovaries (9.9%) and cervix (1.1%). This was followed by breast (14.5%). These findings were similar to the result of the study conducted in Thailand by Mahasittiwat P et al. where gynecological cancers (30.6%) and breast cancers (26.2%) scored the first two ranks among observed tumor types.[20] A study by Chowdhary G et al. conducted in India revealed that the maximum number of cases were from gynecology (28.9%) followed by breast carcinoma (22.7%).[21] The prevalence of anemia was varied by tumor type. Our study demonstrated that 81.8% of gynecological and 93.9% of colorectal cancer patients were anemic. This is higher than the report in Europe and Australia which revealed 49.1% and 65% of gynecological cancer patients were anemic at enrollment.[22,23] This may be attributed to the difference in definition of anemia and study design used. In our study, the severity of anemia was classified according to the National Cancer Institute Classification and maximum number of patients were found to have grade 2 or moderate anemia (34.1%) followed by grade 1 or mild anemia (24.4%); 18.2% patients had grade 4 or life threatening anemia. This was similar to findings in study by Chowdhary G et al. where 27.6% were moderately and 13.4% were severely anemic.[21] Hemoglobin levels were seen to further deteriorate with advancing stages of disease i.e patients of stage III and stage IV malignancies were observed to have moderate to severe anemia. In the advanced stages of hematological malignancies, bone marrow involvement often leads to progressive anemia. In addition, interaction between tumor cell populations and the immune system can lead to the release of cytokines, especially interferon-γ, interleukin-1 and tumor-necrosis factor-α. This release disrupts endogenous erythropoietin synthesis in the kidney and suppresses differentiation of erythroid precursor cells in the bone marrow. As a result, patients with tumor related anemia can have relatively low levels of erythropoietin for the grade of anemia observed.[24] Ludwig H et al.[17]

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

reported that across most tumor types evaluated, a high prevalence of iron deficiency and moderate to severe anemia was noted in pancreatic (63.2%), colorectal (52.2%) and lung cancer (51.3%) patients. In patients with solid tumors, a significant correlation between tumor stage and anemia was found ($P < 0.0001$ and $P < 0.0001$, respectively). The prevalence of anemia increased from 35.4% in stage I – II to 45.2% in stage III and 53.6% in stage IV patients. The corresponding figures for anemia in our study was 18.4%, 29.8% and 41.2%, respectively. In our study, we evaluated the most common etiology of anemia in cancer patients. Out of the 82 patients with anemia, 73 patients (89%) had microcytic hypochromic anemia. Out of these 73, 68 patients had low serum iron and serum ferritin levels, and were classified as iron deficiency anemia and the rest were classified as anemia of chronic disease. 7 patients (8.5%) had macrocytic anemia and low levels of serum vitamin B12. Rest of the patients had anemia of normocytic normochromic type (2.4%). Thus our study observed iron deficiency and anemia of chronic diseases to be the most common etiology. Xu H et al. found that approximately 10% of anemic patients were either microcytic or macrocytic; and around 10% of patients were hypochromic. Findings of the present study was supported by Kanuri G et al.[25] They reported that the etiology of cancer related anemia in their setting was mostly iron deficiency. Aapro M et al.[26] also found that the major etiology of anemia in cancer patients was iron deficiency superimposed by anemia of inflammation. Our findings have also been well supported by Goodenough LT et al. They reported that the major contributor appears to be iron restricted erythropoiesis resulting from anemia of inflammation, absolute iron deficiency or a combination of the two.[27] Iron deficiency was also seen to be highly prevalent in cancer patients in a study by Ludwig H et al.[17] These data indicate that pre-existing micronutrient deficiencies (e.g. iron deficiency) profoundly influence the development of cancer related anemia, in addition to chemotherapy and tumor cell-released cytokines. A comprehensive evaluation of anemia as well as the underlying conditions like the nutritional status and bone marrow function helps to guide anemia management. Ludwig H et al.[17] also observed that across most tumor types evaluated, a high prevalence of Iron deficiency anemia was noted. Iron deficiency was highest in pancreatic (63.2%) and colorectal cancer (52.7%). Marks PW et al.[28] reported that anemia of cancer may also be evident at initial diagnosis. Activation of the immune system appears to be the driving force for a global diminution of erythropoiesis and analogous to chronic inflammatory conditions observed in anemia of chronic disease. Patients with cancer may develop anemia secondary to poor nutrition in general or due to reduced function in the gastrointestinal (GI) tract to absorb nutrients. Iron deficiency anemia may be due to blood loss or the inability to absorb iron in the GI tract and it often occurs in patients with malignancies of the GI tract, including colorectal cancers. Birgegard G et al. also reported similar findings.[18] These findings were similar to our study. Our study indicated that patients with bleeding history were at a higher risk to develop anemia than those patients lacking bleeding history. This finding is similar to studies in India by Bahl A et al.[30] and in China by Gao F et al.[14] which revealed that bleeding from tumor was a major contributing factor for the occurrence of anemia in patients with solid malignancies. In our study, majority of gynecological tumor patients with anemia had a history of bleeding (93.3%)

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

which was a contributing factor for the higher anemia prevalence observed among these tumor types. The mean trigger hemoglobin level for initiating transfusion in our data was 7.7 g/dl, which is lower as compared to reports made by Achariyapota V et al. where mean trigger hemoglobin level for initiating transfusion was 9.5 g/dl.[31] Ludwig H et al. in his study initiated transfusion at mean hemoglobin level of 8.6 g/dl.[12] The possible justification for the low mean trigger hemoglobin level for initiating transfusion in our study is due to variation among doctors` decision in initiating anemia supportive treatment and also as a result of high frequency of Grade 3 anemia when compared to other findings. Regarding the anemia treatment patterns, our data showed that anemia was treated in 32% of patients. This result was similar with study of Ludwig H et al.in which 38.9% of patients were treated for their anemia before commencing anti-tumor agents.[12] In Mahasittiwat P et al's study, 22.3% of patients with anemia got it corrected prior to commencing anti-cancer treatment, which was lower than our study.[20] The most commonly used supportive treatment for anemia correction in our study was blood transfusion (25.8%), which is in agreement with that of studies of Ludwig H et al and Seshadri T et al. (36%).[12,23]

CONCLUSION

The present study has shown that the main etiology of anemia in Indian cancer patients is iron deficiency. It is a widespread and serious problem especially among gynecological, colorectal, lung and breast cancer patients. Its early evaluation and management could reduce the incidence of treatment-related anemia in cancer patients. Newer cancer treatment protocols should be designed keeping in mind the high prevalence of anemia in cancer patients. Measures directed towards characterization and treatment of anemia should be incorporated as an integral part of cancer management protocols. Patients with anemia should be closely monitored, and a vigilant management strategy should be implemented to reduce the risk of morbidity associated with anemia. Quality of life of such patients should also be assessed. Unfortunately, except for pain evaluation, such assessments are infrequent in clinical practice, even at palliative care centers. More than pain, anemia is a factor that can be dealt with to improve the quality of life of cancer patients.

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ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

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