International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2017): 7.296

Anaemia in Patients with Malignant Neoplasms

Maha Abubakr Feissal Rabie

Department of Medical Laboratory Technology, Pharos University in Alexandria, Egypt

Abstract: ***Objective: To evaluate anaemia in Egyptian patients with malignant neoplasms. Methods: This is a prospective study, involved 60 malignant neoplasms' patients (30 males and 30 females) referred from Alexandria University Hospital and the Medical Research Institute in Alexandria for six months (from Jun. 1st to Dec. 30th, 2017). Results: Anaemia among solid tumors was higher than in hematological malignancies. Males showed higher anaemia with hematological malignancies while females showed higher anaemia with solid tumors. Common cancers with anaemia were GIT cancers, breast and leukemias. In males, common cancers with anaemia were GIT cancers, leukemias and lymphomas, while in females, breast cancers, GIT cancers and gynecological cancers. The common morphology of anaemia was normocytic normochromic followed by microcytic hypochromic pictures. The common grades of anaemia were grade 1 and 2, severe degree anaemia was in 21.7%. Anaemic patients with cancers showed significantly lower mean Hb, RBC count, Htc and MCHC, and significantly higher mean serum ferritin and B12 concentrations. Conclusion: This study concluded that anaemia is a common finding in cancer patients and attributed to increased RBCs destruction and cytokins mediated decreased production and recommended further studies.***

Keywords: Cancer – Anaemia – Hematological malignancies – Solid tumor

1. Introduction

Anaemia is a common complication of malignancy, occurring in over 50% of patients.[1] It is defined as an inadequate circulating level of hemoglobin or RBCs, and may arise as a result of the underlying disease, chemotherapy, or radiation therapy.[2]

Anaemia is associated with its own set of debilitating signs and symptoms and can have a significant effect on morbidity and mortality, as well as on the level of care that patients require, despite this knowledge, anaemia may not be optimally managed in the cancer patients' population, the underlying issues that contribute to this suboptimal care may be related to the failure of many clinicians to recognize the impact that anaemia has on the lives of their patients and the inadequacies of current treatment options.[1,2]

However, the continuing development of novel erythropoietic agents,[3] progress in defining parameters to better predict a patient's response to anaemia treatment,[4] along with emerging data that consider the effect of anaemia on end points such as survival and cognitive function,[5] may help to overcome these issues, such initiatives suggest a promising future for the optimal management of anaemia in the cancer patients.

This study was conducted with the aim of raising awareness about current knowledge and practice in management of anaemia in patients with malignant neoplasms.

2. Patients and Method

This was a prospective study for 60 anaemic patients with malignant neoplasms referred from the Hematology Department and the Oncology Department of Alexandria University Hospital and the Medical Research Institute in Alexandria for six months (from Jun. 1st to Dec. 30th, 2017). Excluding patients with malignant neoplasm already on chemo and/or radiotherapy, patients received supplement therapy or blood transfusion during the last three months of presentation.

Patients are subjected to the followings; complete history taking, thorough clinical examination with special focus on the signs and symptoms of anaemia. Abdominal ultrasonography, CT scan of neck, chest, abdomen, pelvis for cancer staging. Routine laboratory investigations, included CBC, blood film, and reticulocyt count. Special tests including serum ferritin, folic acid and vitamin B_{12}.

Anaemia was defined according to WHO definition (Hb <13g/dl in men and <12g/dl in women) and classified into mild, moderate and severs according to WHO classification.[6] The grade of anaemia was classified into 0 to5 according to the NCI classification.

3. Ethical Consideration

The study was performed to achieve a social benefit and for the well being of the humanity. The study design was clearly formulated in protocol and was conducted under supervision of competent clinical professionals. Every participant in the study was assured with sufficient information about the study objectives, content of the questionnaire and possible benefit and risk. Verbal consents were obtained before blood sampling.

Statistical analysis

The statistical analysis was done by using the statistical software package SPSS version 24. Data were first tested by the Kolmogorov–Smirnov test which showed a normal parametric distribution, then parametric tests were applied. Chi-square or Fisher exact tests were used to identify the presence of significant difference between groups having qualitative variables. Student t-test was used for the presence of significant difference between 2 groups having quantitative variables (mean SD). P-values of ≤ 0.05 were considered statistically significant.

4. Results

The involved 60 anaemic patients with different malignant neoplasms. They were 30 male and 30 female patients. The studied patients with anaemia were having solid tumors 41(68.3%) more than hematological malignancies

19(31.7%%). In regard to sex of patients, it was found that male patients reported significantly higher percentage of hematological malignancies (HM) than solid tumors. While female patients reported significantly higher percentage of solid tumors. Even the ratio of male to females showed similar significant pattern of distribution (p<0.05). [Table 1]

Table 1: Distribution of patients with malignant neoplasms by sex and type of malignant neoplasms

Type of malignant neoplasm	Male		Female		Mean age (years)		M : F ratio
	№	%	№	%	№	%*	
Solid tumors (n=41)	17	41.5	24	58.5	54.9 ± 17.5 (18 – 80)		1 : 1.4
Hematological malignancies (n=19)	13	68.4	6	31.6	38.8 ± 18.8 (16 – 65)		2.2 : 1
Total	30	50.0	30	50.0	50.1 ± 19.2 (16 – 80)		1 : 1
M:F ratio: male to female ratio. [χ^2 = 4.59, p = 0.032] Statistically significant.							

The common type of the studied malignant neoplasms with anaemia were GIT cancers followed by breast cancers and leukemias. The remainders were lymphomas, gynecological and myeloma. In male patients, the common malignant neoplasms after GIT cancers were leukemias and lymphomas, while in female patients, the common malignant neoplasms with anaemia were breast cancers, GIT cancers followed by gynecological cancers and lymphomas. [Table 2]

Table 2: Diagnosis of the studied malignant neoplasms with anaemia by sex

Diagnosis	Male (n = 30)		Female (n=30)		Total (n = 60)	
	№	%	№	%	№	%
Gastrointestinal cancers	11	36.7	8	26.7	19	31.7
Breast cancer	—	—	10	33.3	10	16.7
Leukemia	8	26.7	2	6.7	10	16.7
Lymphoma	3	10.0	3	10.0	6	10.0
Gynecological cancers	—	—	5	16.7	5	8.3
Multiple myeloma	2	6.7	1	3.3	3	5.0
Bronchogenic carcinoma	2	6.7	—	—	2	3.3
Other malignant neoplasms	4*	13.3	1**	3.3	5	8.3
*Include 2 neuroblastoma and 2 nasopharyngeal carcinoma ** Include parotid gland cancer						

Hematological parameters in the studied anaemic patients with malignant neoplasms showed that the mean Hb, RBC count and hematocrit were significantly lower among anaemic patients with solid tumors than in hematological malignancies (p<0.05). Serum ferritin concentration showed higher value among anaemic patients with solid tumors than those with hematological malignancies, but without significant statistical variation (p>0.05). [Table 3]

Table 3: Hematological parameters of malignant neoplasms' patients with anaemia by the type of malignancy

Parameter	Solid tumors (n= 41)		HM (n = 19)		p-value
	Mean	SD	Mean	SD	
Hemoglobin concentration (g/dl)	7.7	2.1	9.4	0.9	0.00001*
Red blood cells count ($X10^{12}$/L)	3.29	1.1	3.97	0.69	0.006*
Hematocrit (%)	26.9	8.1	32.9	4.9	0.001*
Reticulocytes count (%)	1.1	0.8	1.3	0.6	0.289
MCV (fl)	82.5	10.8	82.9	11.3	0.905
MCH (pg)	26.5	4.3	25.9	3.3	0.545
MCHC (g/dl)	31.4	1.8	30.5	2.6	0.194
Serum ferritin (ng/mL)	418.2	338.8	284.1	97.0	0.154
Serum folic acid (ng/mL)	12.1	18.3	12.0	10.1	0.991
Serum vitamin B_{12} (pg/mL)	832.9	552	757.6	449	0.153
SD: standard deviation Hb: hemoglobin MCV: Mean corpuscular volume MCH: Mean corpuscular hemoglobin MCHC: Mean corpuscular hemoglobin concentration *p-value < 0.05 is statistically significant					

In anaemic patients with solid tumors, the common morphological type of anaemia was normocytic normochromic anaemia, while in anaemic patients with hematological malignancies the common morphological types were normocytic normochromic and microcytic hypochromic anaemias. About 58.5% of anaemic patients with solid tumors were in grade 0 and I, while 52.7% of anaemic patients with hematological malignancies were in grade 3 and 4 (p<0.05). Severe degree of anaemia was statistically significantly higher in anaemic patients with hematological malignancies (52.6%), while moderate degree of anaemia was significantly higher in anaemic patients with solid tumors (58.5%). [Table 4]

Table 4: Characteristics of anaemia in malignant neoplasms' patients by the type of malignancy

Characteristics of anaemia	Solid tumors (n= 41)		HM (n = 19)		Total (n= 60)	
	№	%	№	%	№	%
- Morphological types of anaemia:						
Microcytic hypochromic	13	31.7	8	42.1	21	35.0
Macrocytic normochromic	5	12.2	2	10.5	7	11.7
Normocytic normochromic	23	56.1	9	47.4	32	53.3
[χ^2 = 0.62 , p= 0.73] statistically insignificant						
- Grade of anaemia:						
0	1	2.4	—	—	1	1.7
1	23	56.1	6	31.6	29	48.3
2	14	34.1	3	15.8	17	28.3
3	3	7.3	4	21.1	7	11.7
4	—	—	6	31.6	6	10.0
[χ^2 = 15.6, p = 0.0004] Statistically significant*						
- Degree of anaemia:						
Mild	14	34.1	4	21.1	18	30.0
Moderate	24	58.5	5	26.3	29	48.3
Severe	3	7.3	10	52.6	13	21.7
[χ^2 =15.8, p = 0.0003] Statistically significant						
* Chi square test was calculated after joining grade 0 with1 and grade 3 with 4						

5. Discussion

Anaemia is common in patients with malignant neoplasms, frequently observed at the time of diagnosis and during treatment. The causes and mechanisms are complex, so that the term "multifactorial" has been applied. Among these malignancies, we observed variable hematological and solid tumors associated with anaemias. However, the percentage

of solid tumors with anaemia was higher in this study. Similar finding was also reported by the study of Ludwig et al (2013),[7] in Austria among 1528 cancer patients. They found that anaemia was detected in 50.4% of patients with solid tumors and 43.7% of patients with hematological malignancies. That is solid tumors are more frequent than hematological malignancies in the frequency of anaemia. This might be attributed to the higher frequency of solid tumors over hematological malignancies, which was evident in previous studies that estimated a ratio of 4 to 1 for solid tumors over hematological malignancies.[8]

The current study showed significant association between patient's sex and hematological versus solid tumors (p: 0.03) with anaemia. It was observed that more males affected with HM (68.4%) and more females affected with solid tumors (58.5%). This is also reported in other studies such as the study of King Abdul-Aziz University Hospital (Saudi Arabia), they reported significant relationship between sex of patients with hematological versus solid tumors and anaemia. In HM, they reported 20 anaemic males out of 27 patients, and in solid tumors they reported 32 anaemic females out of 46 patients.[9]

In the current study, the common malignant neoplasms with anaemia were GIT cancers, breast cancers, and leukemias, followed by lymphomas, gynecological and myeloma. This is not due to the preponderance of anaemia in such cancers, however, it is running parallel to the locally reported distribution of common cancers in Egypt.[10] Cancers of the GIT were also common types to be presented by anaemia in China. In the study of Gao,[11] among 1133 solid tumors, they reported the common cancers with anaemia as gastric cancers (38.02%), colorectal cancers (23.13%) and hepato-pancreato-biliary cancers (22.06%).

Dicato et al (2010),[12] reported that inflammatory cytokines such as tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6), play a major role in the pathophysiology of anaemia in the cancer patient not only through complex mechanisms of the purely inflammatory situation but also through genetic regulatory aspects of erythropoiesis via GATA-1 and GATA-2, and other factors. Because cytokins can induce iron sequestration and decrease RBC production, it can affect the morphology of the produced RBC. In the current study, blood films were carefully examined for every patient and the common morphological type of anaemia was found to be normocytic normochromic picture. This may reflect the early stages of cancer that are associated with low levels of cytokins production. In late stages of cancer; the percentage of normocytic normochromic picture decreases with slight increase in the percentage of microcytic hypochromic picture. This may reflect the time of increased levels of cytokins production with decreasing availability of iron to the RBC production that result in microcytic hypochromic picture in addition to impaired iron homeostasis associated with chronic disease, chronic blood loss and nutritional deficiencies (e.g. cancer-induced anorexia).[13]

Anaemia definitions vary internationally, with the World Health Organization and the US National Cancer Institute classifying anaemia by grade (0-4, with 0 representing "normal" and 4 the most "severe"). In these classification schemes, more severe anaemia grades are identical in terms of Hb thresholds (6.5-7.9 g/dl for grade 3 <6.5 g/dl for grade 4), but less severe grades are identified by slightly different Hb thresholds. In the current study, we classified anaemia according to the US National Comprehensive Cancer Network (NCCN) which defined anaemia as mild (Hb <10-11 g/dl), moderate (Hb 8-10 g/dl), and severe (Hb < 8 g/dl), and we found 21.7% of our anaemic cancer patients with severe anaemia. This severe anaemia was significantly higher among hematological malignancies more than in solid tumors, (52.6% vs. 7.3%).

Similar to our finding, Ludwig et al,[7] reported moderate to severe anaemia to be higher among hematological malignancies more than solid tumors (31.2% vs. 29.7%). The studied patients were not seen before cancer affection, and no documents explained the previous hematological parameters. The changes in hematological parameters were attributed to the present pathology since all of them reported clinical well-being just before the diagnosis of cancer.

Serum ferritin was found higher among anaemic patients with malignant neoplasms. This finding was reported previously by Omari et al,[14] in their study among newly diagnosed patients with lymphomas and they suggested that higher ferritin level may indicate the increase of erythropoietin activity.

Factors leading to high ferritin levels in malignancies can include: inflammatory response in malignancy leads to anaemia and iron accumulation in the reticuloendotelial system. Tissue necrosis can cause direct release of cytosolic ferritin and can increase ferritin levels. Experimental data revealed that ferritin is cleared from the circulation by liver parenchymal cells. Dysfunction due to liver disease can lead to prompt decrease in clearance and serum ferritin levels will rise. Ferritin synthesis in malignant cells can show qualitative and quantitative abnormalities.[15,16]

In the current study, it was found that serum folic acid is significantly low in anaemic patients with cancer. This finding was reported by different previous studies.[17,18] Our finding in serum folic acid was consistent with these studies and it may confirm the role of folic acid as a protective agent in some cancer development which was suggested by the study of Stevens et al,[19] among colorectal cancers.

6. Conclusion and Recommendation

This study concluded that anaemia in Egyptian cancer patients is not due to nutritional deficiency of iron or B_{12}, however, it may be attributed to other pathophysiological mechanisms such as increased destruction of red blood cells and decreased production of functional red blood cells that was mediated through inflammatory cytokins. It is recommended that further studies should be conducted with a large sample size in a national pattern in Egypt.

References

[1] Bokemeyer C, Oechsle K, Hartmann JT. Anaemia in cancer patients: pathophysiology, incidence and treatment. Eur J Clin Invest. 2005;35 Suppl 3:26-31.
[2] Tanaka T, Nakajima M, Abe F, Kawata S, Takahashi K. Anaemia of cancer improving/prophylactic agent. Google Patents. Patent 9,539,225.; 10 Jan., 2017.
[3] Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Br J Cancer. 2001;84 Suppl 1:3-10.
[4] Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer. 2007;43(2):258-70.
[5] Littlewood TJ, Cella D, Nortier JW. Epoetin Alfa Study Group.. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non platinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001;19:2865-74.
[6] Kapur D, Agarwal KN, Agarwal DK. Nutritional anaemia and its control. Indian J Pediatr. 2002;69(7):607-16.
[7] Ludwig H, Muldur E, Endler G, Hubl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anaemia. Ann Oncol. 2013;24(7):1886-92.
[8] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
[9] Al-Ahwal M, Al-Sayes F. Febrile neutropenia comparison between solid tumors and hematological malignancies. Pan Arab Med J. 2005;2(4):4 –7.
[10] Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.
[11] Gao F, Cheng K, Zhao F, Chen Y, Li LH, Dong H, et al. Prevalence and characteristics of anaemia in patients with solid cancers at diagnosis in southwest China. Asian Pac J Cancer Prev. 2011;12(11):2825-8.
[12] Dicato M, Plawny L, Diederich M. Anaemia in cancer. Ann Oncol. 2010;21(suppl_7):vii167-vii72.
[13] Grotto HZ. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. Med Oncol. 2008;25(1):12-21.
[14] Omari S, Khalafallah A, Ayesh M, Matalka I, Al-Hadithi R. High serum erythropoietin and ferritin levels in conjunction with anaemia response in malignant lymphoma. Mediterr J Hematol Infect Dis. 2011;3(1):e2011018.
[15] Min Pang B, Connor J. Role of ferritin in Cancer Biology. J Cancer SciTher. 2015;7:155-60.
[16] Erbaycu AE, Hayriye U, Gülpek M, Tuksavul F, Kalencİ D, Güçlü SZ. The contribution of serum ferritin, iron, iron binding capacity and bronchoalveolar lavage ferritin levels in differential diagnosis of lung cancer from benign pulmonary diseases. Inter J Hematol Oncol. 2007;27(4):129-37.
[17] Nacci A, Dallan I, Bruschini L, Traino AC, Panicucci E, Bruschini P, et al. Plasma homocysteine, folate, and vitamin B12 levels in patients with laryngeal cancer. Arch Otolaryngol Head Neck Surg. 2008;134(12):1328-33.
[18] de Vogel S, Meyer K, Fredriksen A, Ulvik A, Ueland PM, Nygard O, et al. Serum folate and vitamin B12 concentrations in relation to prostate cancer risk--a Norwegian population-based nested case-control study of 3000 cases and 3000 controls within the JANUS cohort. Int J Epidemiol. 2013;42(1):201-10.
[19] Stevens VL, McCullough ML, Sun J, Jacobs EJ, Campbell PT, Gapstur SM. High levels of folate from supplements and fortification are not associated with increased risk of colorectal cancer. Gastroenterology. 2011;141(1):98-105, .e1.

Author Profile

Dr. Maha Abu Bakr Feissal obtained BSc. in Medicine from Alexandria University, Egypt 1999. Master degree in Clinical pathology from Faculty of Medicine, Alexandria University, 2004 and M.D in Clinical Hematopathology from Medical Research Institute, Alexandria University, Egypt 2017. Working now as Lecturer in the Department of Medical Laboratory Technology, Pharos University in Alexandria, Egypt.