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Assessment of severity of anemia and its effect on the quality of life (QOL) of patients suffering with various types of neoplasia

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Abstract
Anemia is one of the most important key factors affecting the quality of life (QOL) which needs addressing, as it is an important domain in optimal QOL. About 60-75% of the cancer patients invariably developed anemia most of them were at advanced stages where treatment options were limited and mainly palliative. In advanced stages of cancer, QOL issues become an integral part of decision- making about various treatment options. Several key factors, including age, gender, co-morbidities, and quality of supportive care affects QOL in patients suffering from neoplasia. Fatigue appeared to exert adverse effect and impact on survival and QOL. Among the wide range of cancers anemia was most prevalent in hematological malignancies, followed by breast cancer, stomach, head and neck cancers. The probable causes that relate to various therapeutic protocols were dealt-with individually along with management strategies. In this study, we have evaluated severity of anemia for the first time in cancer patients and correlated its impact on QOL and survivability rates. As this study is limited to represent only a few types of carcinomas of different origin, many surveys that are more extensive are required to comment on the poor QOL of cancer patients burdened with anemia.

Keywords: Anemia, Cancers, QOL, chemo and radiotherapies, nutritional factors, haematopoisis, CBP, Pathological diagnosis, CRF, Drugs.

Introduction

Assessment of the QOL of patients can provide important clinical information to physicians, especially in the area of oncology. QOL becomes increasingly important in understanding and approaching the overall management of cancer patients. The tools available to clinicians and researchers to assess QOL will continue to evolve, as neoplasia is associated with a low rate of long-term survival and a range of painful and debilitating symptoms. Various self-report questionnaires have been developed to monitor QOL like EORTC QLQ-C30, Linear analogue scale assessment (LASA) as well as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale. It is believed that QOL assessment should be an integral part of cancer clinical trials; however, investigators must acknowledge the difficulties in collecting this type of data. The development of new instruments and the refinement of old ones will facilitate the collection of data for this important aspect of clinical trials research (Ganz PA et al, 1988).

Improving quality of life (QOL) in oncology patients is an important therapeutic goal, and most treatment decisions are heavily influenced by their effect on QOL. Although measuring QOL has been a significant challenge because of a lack of consensus on the definition of QOL, research in this field has advanced rapidly (Soni MK, Cella D, 2002). Quality-of-life has been found to be significantly positively related to hemoglobin level in anemic cancer patients. This suggests that normalization of hemoglobin in cancer patients is likely to increase their quality-of-life (M. Lind et al., 2002). A subsequent study identified hemoglobin level as a variable important in optimal quality of life. Dr. Charles Cleeland and colleagues (Cleeland CS et al., 1999) reported the results of an incremental analysis that related hemoglobin levels to quality of life.

Hematopoiesis depends on the smooth functioning of three factors, i.e., the continuing presence of stem cells that are capable of differentiating and develop into mature blood cells or bone marrow, which supports the stem cell survival and functioning and a complex system of highly regulated haematopoietic growth factors that regulate the proliferation, differentiation and survival of blood cells.

Anemia results when this system fails to function properly. It is a disease by itself or can be due to various therapies in cancer treatment. It is often a significant contributor to symptoms in persons with cancer (Johnston E, 1998) a common complication of malignancies and thus forms a basis to access QOL. Since it causes complex complications, the term 'multifactoral' has been applied (Hussain I. Saba, 1998).

Cancer therapeutics such as radio and chemotherapies act as alkylating agents and lead to progressive depletion of hematopoietic stem cells in the bone marrow. This may lead to long-term anemia, which make the treatment less effective. Some chemotherapeutic drugs, such as anthracyclines, can damage mature red cells by oxidation, there by shortening of the red cell life span by 60 and 90 days (Andrews NC, 2004). The factors responsible for anemia in cancers include, the neoplastic process itself, due to products of the cancer circulating in the blood or may be due to the cancer treatment (Table I). These effects may be reflective of a paraneoplastic syndrome (Hussain I.Saba 1998) or intercurrent infections, clonal disorders of hematopoiesis, gastrointestinal blood loss, autoimmune hemolysis, microangiopathy, excessive marrow fibrosis and displacement, Iron, folate, vitamin B12 deficiency and renal impairment etc (Ludwig H, Fritz E, 1998). Several cytokines, including tumor necrosis factor (TNF), Interferon Gamma (IF γ) and Interleukin-1 (IL-1), released into the blood of cancer patients can suppress erythropoiesis by affecting red cell production and impaired iron utilization (Ernest H. Rosenbaum, 2003) (Table II) . Inflammatory cytokines promote the production of WBC's. Bone marrow produces both RBC's and WBC's from the same precursor stem cells. Therefore, the up regulation of WBC's causes fewer stem cells to differentiate into red blood cells. This may be an important cause for the effective inhibition of erythropoiesis, even when erythropoietin levels are normal (Caro JJ et al., 2001).

Direct-acting factors in cancer patients are exogenous blood loss, intratumor bleeding, erythrophagocytosis or bone marrow replacement. Notable among these are solid tumor malignancies, such as breast and prostate cancer, which invade the marrow. Often overlooked as factors in inducing anemia, these malignancies produce a desmoid or fibrotic reaction, with increased marrow fibrosis that results in alteration of marrow space and sinusoidal matrix. This can affect the orderly release of mature blood cells from bone marrow and can produce a leucoerythroblastic picture with immature red cells and early myeloid white cells seen in peripheral blood. The development of antibodies in chronic lymphocytic leukemia, lymphoma, and sometimes, solid tumor malignancies can lead to immune hemolytic anemia. Furthermore, development of microangiopathic hemolytic anemia may result from procoagulants released from cancers (Hussain I. Saba, 1998).

The clinical consequences of anemia relate to the cytokine-associated variations. Tumor necrosis factor (TNF) increases in patients with cancer. Furthermore, injection of TNF in human patients with metastatic cancer results in the expression of all the features of impaired iron utilization. Cytokines such as IL-6 & TGH-β also suppress erythropoiesis and iron metabolism, but their exact role has not yet been determined. Thus, it appears that, anemia in cancer patients is a 'cytokine-associated syndrome' in which multiple cytokines interact to produce suppression of erythropoiesis and derangement of iron metabolism [6]. Anemia is associated with poorer prognosis and increased mortality. In a systematic review of 60 papers, Caro and colleagues examined the survival of cancer patients according to either Hb levels or the presence of anemia and found that the relative risk of death varied by cancer type. Overall, the presence of anemia in cancer patients increased the relative risk of death by 65% ((Ernest H. Rosenbaum, 2003).

One of the ways anemia increases mortality is by influencing treatment efficacy. Anemia influences response to radiation therapy because it limits the oxygen-transporting capacity of the blood and consequently tissue oxygenation. Thus, anemia can contribute to tumor hypoxia, which makes solid tumors resistant to sparsely ionizing radiation and some forms of chemotherapy (Vaupel P et al, 2001). In contrast, well-oxygenated tumors have a greater chance of being controlled (Shasha D, 2001, 2004 & 2006). Many studies have documented the association between anemia and poor outcome in cancers of the head and neck, respiratory tract, pelvis and genitourinary organs (Kumar P, 2000).

In view of the above clinical consequences of anemia in patients already suffering from the burden of cancers, we have undertaken this investigation, in order to look for parameters, which can improve their QOL. It is seen that 60% of cancer patients have anemic

conditions with a negative effect on quality of life and requiring blood transfusions; anemia is associated with decreased survival, decreased tumor response, delays in therapy, reduced patient compliance, and directly retracts from patient's therapeutic outcomes. Hence, to understand these factors and develop appropriate management strategies for the benefit of the patients and to improve QOL we decide to investigate anemia of cancers.

Materials and Methods

Study group and sample collection

The study group consisted of 100 anemic individuals of both the sexes diagnosed with neoplasia of various kinds by the Oncologists of the Hospitals. The enrollment of cancer patients with anemia was in accordance with the ethical standards of the responsible committee of the Hospital to participate in this investigation. Further, patients' consent as voluntary participants in this investigation was obtained. The study group was of South Indian origin and of a particular region i.e. Andhra Pradesh. At the time of enrollment, their medical history and the kind of neoplasm they were suffering from, was recorded and all data was subjected to statistical analysis. Blood samples collected from the patients were used for anemia typing and various other investigations. Standard Procedures were used for biochemical and hematological investigations.

There are varying degrees of severity of anemia, typically based on hemoglobin levels. We used the NCCN anemia classifications to rate the severity of anemia. The National Comprehensive Cancer Network (NCCN) utilizes these classifications of anemia to determine appropriate therapy.

Diagnosis and recording of pathological data

At the time of admission, the study group included in this investigation were routinely diagnosed for the following parameters like name, age and sex, general health, symptoms of fatigue and other illness, blood test, pathological tests, diagnosis and determining the type of cancers, nutritional status etc. Data on chemotherapy was noted from the records. All the tests carried out for these patients were standard procedures routinely used in the diagnostic laboratory with quality control and systematic recording of the required details. Histopathological data determined the type of cancer (Benign or Malignant). Oncologists determined the type, grade and stage of cancer and biochemical investigations determined the complete blood picture. Several other tests were also carried out on these patients but they are not relevant to this investigation, hence not included but reported elsewhere (Haranatha Reddy and Kaiser Jamil, 2006, Rama Mani et al, 2006). Wherever required, statistical and computational methods were employed.

Results

Quality-of-life endpoints are being increasingly incorporated into clinical trials of newer agents to further define meaningful response. The assessment of QOL involves comprehensive measurement tools that address the physical, social, functional, and emotional well-being of the patient. Such measurements should be easy to use, meaningful, and relevant to the patients and clinician. Although these measures assess the longitudinal impact of treatment on QOL, pretreatment QOL scores may also be an important prognostic factor for survival in patients.

The cases that we have investigated were randomly enrolled in this study as per their voluntary confirmations. The characteristics of the patients are presented in Table-III. Most of the cases were anemic at the time of initial diagnosis (pre-operative, Table-III) except breast cancer cases where postoperative conditions and chemotherapy might have led to anemic conditions (Table- III). This is our preliminary study on anemia in cancer patients and relates to our first attempt to examine various types of cancer patients burdened with additional suffering from fatigue due to anemic conditions.

It is seen from the table III that in this study group of 100 anemic patients the statistics showed that anemia occurs mostly in hematological malignancies (especially ALL), followed by breast cancer, stomach and gastro-intestinal cancer and then by head and neck cancers. Ovarian and cervix cancers were about 8% and 7%. This study had no patients with lung cancer, colon cancer or other types of cancers (Table-III and Fig- I). Several of our subjects received blood transfusions. Some of these cases were very severe and some were follow-up cases. The following table IV indicates the picture of a few cases (about 23) of various types of cancers, the transfusions taken by patients and the severity of anemia that is associated with these cancers. In this table, we have included parameters like age, sex, type of cancer, number of transfusions received by the

patients and the severity grading of anemia (Table-IV).

From the cases listed, it is seen that patients with hematological malignancies received the highest number of transfusions ranging from 5 units to 44 units, where one case of ALL-L_1 received 44 transfusions with 27 units of random donor platelets and 7 units of PRC with little or no effect. The next significant cancer associated with anemia was breast cancer where the number of transfusions given to the patients ranged from 2 units to 26 units. In addition to the transfusions the patients with anemia were given supportive treatment with drugs like neukine, neupogen etc to stimulate the proliferation and differentiation of granulocytes and a very few patients were administered with epoetin- α. These patients were treated with various combinations of drugs as required for the disease conditions. The hemoglobin levels of these patients (minimum and maximum) are presented in Figure –II. However, chemo drugs administered and their dosage levels or the frequency of their treatment etc is not included.

Anemia in cancers is promoted by the cellular immune system and inflammatory changes, which stimulate the production of chemicals called 'cytokines' that affect both red cell production and survival. Approximately 75% of all cancer patients reported symptoms of fatigue (weakness, listlessness, low energy, trouble starting, finishing tasks, and the need to sleep during the day), which is the primary symptom of anemia. A range of other symptoms includes pallor, palpitations, impaired cognitive function and immune function, nausea, dizziness, headache, shortness of breath, chest pain, and increased heart rate. These can compromise a patient's ability to tolerate treatment and may severely interfere with activities of daily living. Risk factors for persistent low energy in cancer patients include older age, advanced disease, and combination-modality therapy.

Table 1: Anemia due to known products of cancer

Substance	Mechanism	Neoplasm
Amyloid	Marrow replacement	Plasma cell dyscrasia
Antibodies	Immune hemolytic anemia	Chronic lymphocytic leukemia, lymphoma, adenocarcinomas
Procoagulant proteins	Microangiopathic hemolytic anemia	Gastrointestinal malignancies (mucin), prostate cancer

(Source: Hussain I. Saba, 1998)

Table 2: The etiological factors contributing to the anemia in cancers and their possible interventions

Factor	Possible Intervention
Blunted endogenous erythropoietin response	Erythropoietin administration
Cytokine induced erythropoiesis suppression IL-1 IL-6 TNF-α	Cytokine inhibitors
Functional iron deficiency	Iron replacement
Chemotherapy induced bone marrow suppression	Erythropoietin
Bone marrow infiltration by cancer	Red blood cell transfusion Erythropoietin
Bleeding	Red blood cell transfusion Erythropoietin Red blood cell transfusion

(Source: Razelle Kurzrock, 2001)

Table 3: Anemic conditions in patients associated with various types of cancers in this study

Type of tumor	Number of Patients (%) n=100	Pre-operative	Post-operative	Hb fluctuations (g/dl)	Anemia grades
Hematological malignancies (NHL, ALL, AML, CML)	45%	0	0	3.2 - 10.5	2, 3, 4
Breast	15%	3	12	6.2 - 9.7	3,4
Stomach & GI	15%	10	5	7.2 - 9.1	1, 3,4
Head & Neck	10%	8	2	2.3 - 7.5	4
Ovary	8%	6	2	5.5 - 11.2	3,4
Cervix	7%	4	3	4.8 – 12.7	3,4

Fig 1: Picture of anemic conditions associated with various types of cancer in this study

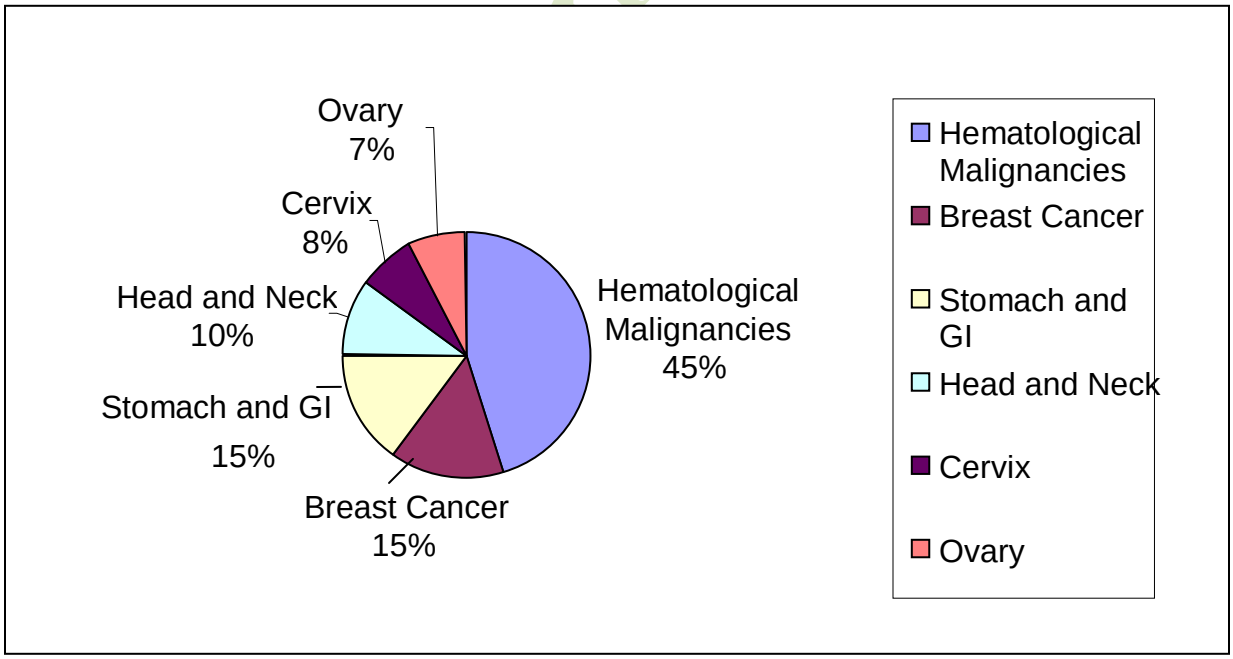


Fig 2: Showing the relation between Hb fluctuations in malignancies and anemia

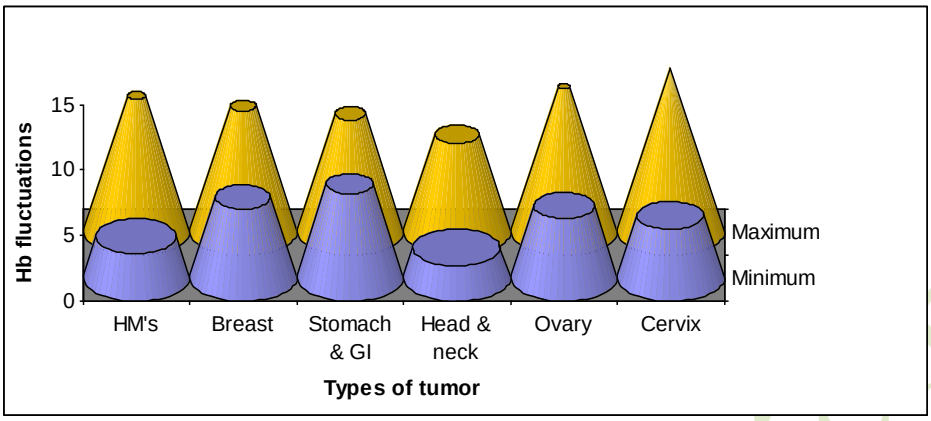
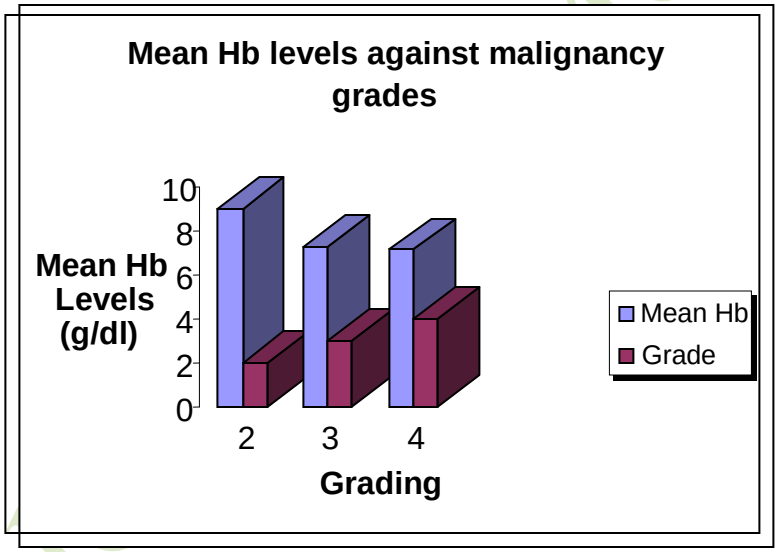


Fig 3: Showing the relationship between the mean Hb levels and the severity grading.



Discussion

The purpose of this study was to evaluate the quality of life of the patients with the advanced cancers. Optimal management of Hb levels contributes significantly to improving the QoL of anemic cancer patients receiving chemo and radiotherapy. A direct relationship exists between hemoglobin increases and corresponding QOL increases. Maximal incremental gain in QOL occurred when hemoglobin was approximately 12 g/dL (range, 11–13 g/dL) (Shasha et al, 2004).

In this study, we found that the impact of anemia in cancers varied depending on factors such as rapidity of onset, patient age, plasma-volume status and the number and severity of co-morbidities. The hemoglobin levels that fluctuated during the course of this investigation showed the head and neck cancer patients were more prone to the adverse effects when compared to the other forms of cancers evaluated here (Figure-II). Blood transfusions and the two available erythropoietic stimulating agents –Darbepoietin-α and epoietin-α were the two therapeutic options used to treat this regimen-related toxicity. Though both agents demonstrated their effectiveness in raising the Hb concentration and potentially reducing the

need for transfusions, the side effects are well known. Red cell transfusions are the old mainstay, which offers the quickest relief for anemia but there are risks associated with transfusions (Ernest H. Rosenbaum, 2003). Nevertheless, repeated transfusions can be cumbersome, and the risks of blood-borne infections can be worrisome for patients.

Many patients react to the white blood cell antigens by developing fever. To prevent this, patients are routinely premedicated. Transfusion is however done cautiously, because of the risks associated with exposure to allogenic blood products. Individuals with long-term transfusion needs (Table-IV) such as patients with leukemia were given blood products with a reduced number of white blood cells to reduce the risk of sensitization to transfused blood. Such therapies are of common practice among clinicians and oncologists (Thackery, Thomson Gale, 2002). Some of the cases were chemotherapy-induced anemia patients. This is one of the most common side effects experienced by cancer patients, occurring in approximately 70%-90% receiving chemotherapy. Recent studies provide a clear picture regarding the physiologic risks associated with anemia, particularly patient outcomes including survival and responses to therapy (Freemantle N, et al, 2005, Hedenus M, et al, 2005, Peters-Engl C, et al, 2005, Juan O, et al, 2005).

Several other factors also influence the severity of anemia secondary to chemotherapy. As anemia develops or tissue hypoxia develops plasma erythropoietin levels and Hb concentration follow an inverse linear relationship (Kristin Crowley, Kristen Augustin, 2003). Most anti-cancer drugs have adverse drug reactions Suman G and Kaiser Jamil, 2006 a,b,&c). Some of the chemotherapeutic agents have suppressive effects on the rapidly proliferating cells of the bone marrow. At least one chemotherapy drug, cisplatin, appears to blunt erythropoietin production and cause prolonged anemia (Cazzola M, 2000). However, certain agents target erythropoiesis to a greater degree. Such agents include platinum and taxane-based regimens as well as combination chemotherapy, which are often administered to treat Non Hodgkin's Lymphoma and breast cancer.

The commonly used combination of cyclophosphamide-doxorubicin-5-FU produced grade 1 or 2 anemia in 55% and grade 3 or 4 anemia in 11% of patients with Metastatic breast cancer (Jerome E. Groopman, Loretta M, 1999). Cisplatin and etoposide, a combination frequently used for the treatment of non-small-cell lung cancer, causes severe anemia in 16% to 55% of patients; however, treatment of advanced colorectal cancer with 5-fluorouracil and leucovorin causes severe anemia in only 2% to 5% of patients (Demetri GD, 2001).It is seen that mutations in drug metabolizing genes (CYP3A4, DPD) influences drug metabolism leading to adverse drug reactions that includes bone marrow suppression in post chemo breast cancer patients and in some invasive ductal carcinoma patients (Suman G and Kaiser Jamil, Kalyan Kumar and Kaiser Jamil 2007). Findings suggest that MTHFR C677T and A1298C gene variants do not have a major influence on susceptibility to breast cancer in south Indian population (Kalyan Kumar and Kaiser Jamil, 2006; Muhammad Khan and Kaiser Jamil, 2008 a, & b) but combined effect between methotrexate and reduced activity of the MTHFR 677C→T polymorphisms occur leading to toxicity (Toffoli G et.al, 2003).

Some cases in this study were under radiation therapy, which induces tissue hypoxia and anemia as seen in head and neck cancers, cervical cancers also reported by Rosenbaum, (2003). The results show that 48% of the patients presented with anemia initially (hemoglobin <12 g/dl) and 57% ultimately became anemic by the end of therapy. When stratified by sex, 32% of men and 57% of women with anemia, showed an increase to 51% and 64% by the end of treatment. In one report, men with prostate cancer experienced increase in anemia during radiation therapy (Bush RS, 1986). This indicates that anemia is a common problem for a majority of patients undergoing radiotherapy.

Nutrition support should be indicated for cancer patients considering the potential effects to improve the QOL. When the cause is obscure and there is no perfect remedy then treatment is supportive. Nutritional interventions including the intake of nutrient rich foods and supplements must be considered in addition to other treatment modalities. A balanced meal can help to replenish lost nutrients and strengthen defenses. This study as well as the evidence provided by other workers suggests that anemia may be a major factor in cancer-related fatigue (CRF) and quality of life (QOL) in cancer patients (Glaspy J et al, 1997). Fatigue exists in 14% to 96% of people with cancer, particularly in individuals actively undergoing treatment (Cella

D et al, 2002). In people with cancer, three major mechanisms may be involved: alteration in the body's ability to process nutrients efficiently, increase in the body's energy requirements, and decrease in intake of energy sources. Causes of nutritional alterations and the strategies to overcome it are generally given by counseling.

Helping patients to maintain an optimal QOL while attempting to control their disease is essential for successful patient management. Because of the correlation between QOL and anemia is one of the key strategies in managing cancer, patients should be timely treated for anemia to alleviate or prevent fatigue. It is best managed by treating the underlying cause like blood loss, nutritional deficiency, cancer, bone marrow infiltration, chronic illness, inflammation or decreased response to erythropoietin. In many cases, treating or removing the cancer corrects the red blood cell deficit. More commonly, cancer-related anemia is treated with blood transfusions and/or a drug called epoietin alfa and other similar dugs. The use of Epoetin alfa in the cancer setting has shown great promise. However, this drug is generally not recommended for use in cancer-related anemia because it causes bleeding, hemolysis, or iron deficiencies, it is not recommended for every patient and especially patients with hypertension or albumin sensitivity (Ellen Thackery, Thomson Gale, 2002). Screening of cancer patients a priori could be feasible approach for avoiding chemo drug toxic effects. It can also be used for the determination of mutation carriers (Kalyana Kumar, Sudha Murthy and Kaiser Jamil, 2007). Well-known proverb 'prevention is better than cure' is the best thing to be followed. Proper awareness and intake of hygienic food may help the patient to cope up with anemic conditions during and after treatment.

Conclusion

Several factors are responsible for anemic conditions in cancers. We have evaluated the possible role of therapeutic procedures and nutritional factors as responsible for anemic conditions, besides simple facts like post-operative conditions. We conclude that the incidence of grade 3 or grade 4 anemia's in non-myeloid malignancies in adults could be due to conventional combination of cytotoxic chemotherapeutic regimens (which is also supported by the chemotherapy trials to document the incidence and severity of chemotherapy-induced anemia). It was also found to be associated with the combined effect of the chemo drugs plus genetic polymorphisms in the drug metabolizing genes (as documented in our earlier studies), leading to hematological toxicity and to anemia. Deficiencies of folate can also cause megaloblastic anemia. We believe that ROS generated by hypoxia conditions, plays an important role in inducing anemia in cancers. The role of circulating biomolecules like interleukins and cytokines needs to be assessed when treating anemia of cancer patients. Hence, it is concluded from this study that besides transfusions of PCV, RBC or platelets, nutritional supplements are to be addressed for improvement in the QOL and increasing the survivability. The promising therapies like epoetin alfa etc are out in the market for those who can afford it and may be unaffordable by the general population in India; also, options of stem cell therapies are not discussed here. Perceptions by clinical oncologists can be overcome as research provides further insight of the root causes of anemia and patients coping with cancer must know that that mild to moderate anemia must be endured without treatment,. These findings emphasize the need for routine patient-based symptom assessment in the clinical setting. Unfortunately, except for pain evaluation, such assessments are infrequent in clinical practice, even within palliative care centers. More than pain, anemia is a factor that can be dealt with to improve the QOL of cancer patients.

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