Cancer-related anemia

Hikmat N. Abdel-Razeq, MD.

ABSTRACT

Anemia is the most common hematological abnormality in cancer patients, unfortunately, it is often under-recognized and under-treated. The pathogenesis of cancer anemia is complex and most of the time multifactorial; involving factors related to the tumor itself or its therapy. While anemia can present in a wide range of symptoms, involving almost every organ, it is believed that it contributes much to cancer-related fatigue, one of the most common symptoms in cancer patients. In addition, there is increasing evidence to suggest that anemia is an independent factor adversely affecting tumor response and patient survival. While blood transfusion was the only option to treat cancer-related anemia, the use of recombinant human erythropoietin (rHuEPO) is becoming the new standard of care, more so with the recent studies demonstrating the feasibility of a single weekly injection. Things are even getting better with the recent approval of a new form of rHuEPO; Darbepoetin, an analogue with a 3-fold longer half-life. In addition to its effect in raising hemoglobin, several well-controlled studies demonstrated decrease in transfusion requirements and better quality of life assessed objectively using standard assessments scales.

Saudi Med J 2004; Vol. 25 (1): 15-20

Anemia is the most common hematological abnormality in cancer patients, occurring in up to 50% of patients during the course of their disease,[1] the prevalence is even higher in patients receiving chemotherapy or radiotherapy.[2-4]

Etiology of anemia in cancer patients. The pathogenesis of cancer anemia is complex, it is often difficult to identify a single direct cause of anemia in patients with cancer, and in most of the time it is multifactorial. While both radiotherapy and chemotherapy can be immunosuppressive and inhibit erythropoiesis, some treatments cause a greater degree of anemia than others. For example, the combination of cisplatin and etoposide for the treatment of small cell lung cancer, produce grade 3 or 4 anemia in up to 55% of the patients, while the combination of 5-FU and leucovorin, for advanced colorectal cancer, produce grade 3 or 4 anemia in <5% of the patients.[5] **Table 1** lists some of the most common causes of anemia in cancer patients. Significant portion of cancer patients with anemia have no identifiable cause; the anemia in this situation is classified as anemia of chronic disease. The underlying mechanisms responsible for this type of anemia are unclear, but are thought to involve the activation of cytokines such as Interferon-γ, Interleukin-1 and tissue necrosis factor (TNF). These cytokines may suppress endogenous erythropoietin (EPO) production, impair iron utilization and reduce erythroid precursor proliferation.[6]

Symptomatology of anemia. Anemia can cause a wide range of symptoms involving almost every organ. The severity of these symptoms depends on several factors such as the degree of anemia, rapidity of onset and co-morbidities. These symptoms range from dizziness and palpitation to pulmonary edema, heart failure, depression and even cognitive impairment.[7] Fatigue is one of the most common symptoms in cancer patients, reported in >75% of the cases.[8,9] It is also the most important factor that adversely affects their quality of life (QOL). In one survey, 78% of 419 randomly selected cancer patients, reported experiencing fatigue during the courses of their disease

From the Department of Medicine, King Fahad Armed Forces Hospital, Jeddah, *Kingdom of Saudi Arabia*.

Address correspondence and reprint request to: Dr. Hikmat N. Abdel-Razeq, Hematology and Medical Oncology Consultant, Department of Medicine, King Fahad Armed Forces Hospital, PO Box 9862, Jeddah 21159, *Kingdom of Saudi Arabia*. Tel. +966 54655930. Fax. +966 (2) 6652469. E-mail: razeq@yahoo.com

or its therapy. Moreover, 61% of the patients indicated that fatigue adversely affected their lives more than cancer-related pain.[10] While cancer fatigue has a different pathogenetic mechanisms, it is believed that anemia is a significant contributing factor.[11] Unfortunately, this issue is not sufficiently addressed by most practicing oncologist.[3]

Anemia as an adverse prognostic factor. Aside from its important role in QOL issues, there is an increasing evidence to suggest that anemia is an independent factor that can adversely affect survival in cancer patient.[12,13] Caro et al,[14] reviewed 60 reported papers of patient's survival with cancer according to their hemoglobin (Hb) level. In this diverse group of cancer patients, anemia increased the overall relative risk of death by 19% in patients with lung cancer, 47% in patients with prostate cancer, 67% in patients with lymphoma and 75% in patients with head and neck cancer. Though there is an accumulating evidence to suggest that anemia adversely affects survival in cancer patients; however, a data regarding improved survival with correction of anemia is conflicting. Tissue hypoxia results from imbalance between oxygen supply and consumption; in solid tumors, the oxygen consumption rate of the neoplastic cells may outweigh oxygen supply and results in tumor hypoxia. Oxygen supply might be limited by inadequate perfusion resulted from the structural and functional abnormalities of the tumor microcirculation, it can also be caused by an increase in diffusion distance. Anemia, caused by the tumor or its therapy, can lead to reduced oxygen carrying capacity of the blood, further contributing to tumor hypoxia. Tumor hypoxia can be a contributing factor in failure of the tumor to respond, as it makes solid tumors resistant to both radiation and chemotherapy. Hypoxia may affect proliferation kinetics and cell cycle position; both can modulate the amount of cells destroyed following radiation or chemotherapy. Studies had also shown that sustained tumor hypoxia can additionally enhance malignant progression and may increase aggressiveness through clonal selection and genome changes.[15] Utilizing a computerized polarographic needle electrode system, the determination of tumor oxygenation in primary or secondary lesions was made possible. The significance of tumor oxygenation for therapy outcome became evident in both experimental and clinical studies.[16,17] Multivariate analysis has shown that hypoxia is a powerful prognostic factor in squamous cell carcinoma of the head and neck,[17,18] cervix cancer,[19-21] and soft tissue sarcomas.[22] Improving tissue oxygenation is believed to enhance therapeutic outcome

Treatment options. Every effort should be made to try to identify the etiology of anemia; treatment should be directed to the underlying cause. However, in most of the cases, it can be difficult to identify a specific causative factor, and directed therapeutic intervention may not be effective. Until recently, blood transfusion (BT) was the mainstay of treatment. While transfusion is still indicated for patients with symptomatic anemia, or severe hemolysis, who requires rapid correction of their Hb and increase in blood volume, the effect of transfusion is short-lived, and may be associated with numerous potential complications.

Recombinant human EPO (rHuEPO). The rate of red blood cell (RBC) production is regulated by EPO, a 165-amino acid glycoprotein hormone. In adults, 90% of the EPO is produced by the kidney, in the peritubular interstitial cells, while the liver accounts for the remaining 10%. The EPO gene, located on chromosome 7, was successfully cloned in 1983,[23] which then led to the development of rHuEPO. Miller et al[24] studied 81 anemic patients with solid tumors; they showed that for any specified degree of anemia, the serum concentration of EPO was significantly lower than in matched group of controls with anemia caused by iron deficiency (p=0.0001). The production of EPO was further blunted in patients receiving chemotherapy.

The use of epoetin alfa in chemotherapy patients. Epoetin has been in use for over a decade to treat anemia associated with cancer and chemotherapy. Several studies have demonstrated that epoetin alfa was effective in increasing Hb level as compared to placebo.[25-27] In one study, Littlewood et al,[28] randomized 375 patients receiving non-platinum chemotherapy regimens; one group received epoetin alfa at a dose of 150 IU/kg, subcutaneously, 3 times per week, while the other group received placebo. The dose was adjusted at 4 weeks according to their response. The mean Hb increase from baseline was significantly greater for patients who received epoetin

Table 1 - Etiology of anemia in cancer patient.

I. Cancer-related
A. Blood loss (GI, GU, GYN)
B. Hemolysis (lymphoma, CLL)
C. Tumor infiltration and destruction of the bone marrow
D. Anemia of chronic disease (cytokines: TNF, interferon, interleukins)
II.Treatment-related
A. Blood loss (surgery)
B. Radiotherapy-induced bone marrow suppression
C. Chemotherapy-induced bone marrow suppression
D. Nephrotoxicity of chemotherapeutic agents (decrease EPO: platinums)
III. Patient-related
A. Age
B. Poor appetite
C. Nutritional deficiency (resection of bowel, stomach)

GI - gastrointestinal, GU - genitourinary, GYN - obstetrics-gynecology, CLL - chronic lymphocytic leukemia, TNF - tumor necrosis factor, EPO - erythropoietin

alfa (2.2 gm/dL) compared with patients who received placebo (p<0.001). Three other large, open-label, clinical trials demonstrated the efficacy and safety of epoetin alfa in more than 7,000 patients.[29-31] In these studies, Hb increased by more than 2 gm/dL in 53-68% of the cases, and reduction in transfusion requirement occurred in 50-75% of the patients enrolled. Quality of life assessment was measured using validated visual analog scale, the linear analog scale assessment (LASA), both at baseline and after 4 months of therapy. Mean score for energy, ability to perform daily activities and overall QOL were significantly higher after epoetin alfa treatment compared with baseline. A recent meta-analysis of 12 clinical trials, involving 1,390 evaluable patients, showed that epoetin led to a 38% reduction in the proportion of patients requiring RBC transfusion compared with those patients in whom epoetin was not used.[32]

Epoetin in patient undergoing radiotherapy. The importance of Hb level for tumor oxygenation and response to radiotherapy was already discussed. The negative impact of anemia on tumor progression in patients undergoing radiotherapy has been well studied in several clinical trials. Cervical, head and neck, bladder and lung cancer are the main tumors studied.[33-37] In one multicenter retrospective Canadian study, 630 patients with cervical cancer who underwent radiotherapy were reviewed. Patients with higher Hb level had significantly lower rate of relapse, local recurrence and distant metastasis. A stepwise, significant increase in overall survival rate was noted as Hb level increases.[38] Epoetin has also been tried in cancer patients with anemia who were not on chemotherapy or radiotherapy. Quirt et al[39] treated 183 such patients with epoetin alfa at a dose of 150 mcg/kg subcutaneously 3 times per week. The dose was doubled if the Hb level did not increase by at least 1 gm/dL after 4 weeks of therapy. Epoetin therapy significantly increased Hb level and reduced transfusion requirements. Moreover, epoetin alfa therapy resulted in statistically significant and clinically meaningful improvement in QOL as measured by Functional Assessment of Cancer Therapy-anemia (FACT-A), and LASA.[39]

Epoetin in multiple myeloma and chronic lymphocytic leukemia. Multiple myeloma (MM), and chronic lymphocytic leukemia (CLL) patients, often develops anemia due to the disease process or its therapy. The first open-label study evaluated the use of epoetin alfa in patients with MM was published in 1990. In this study, 13 patients with Hb <11gm/dL, whom had previously received chemotherapy, were treated with epoetin alfa at a starting dose of 150 IU/Kg, 3 times per week. Eleven of the 13 patients (85%) responded to treatment with a median response time of 5 weeks. No significant side effects were reported.[40] A randomized, placebo-controlled study of 132 MM patients on chemotherapy, showed a significant decrease in the percentage of patients transfused when epoetin alfa was administered at the above dose and schedule, compared with patients on placebo. A significant increase in Hb level was also observed in the epoetin alfa group.[41] Two other randomized trials in patients with CLL, MM and non-Hodgkin's lymphoma (NHL), reached similar conclusions.[42,43] In the absence of strong clinical evidence to support the routine use of epoetin in MM and CLL, it is reasonable to begin the treatment with chemotherapy and observe the hematological outcome achieved through tumor reduction. If a rise in Hb level is not achieved with chemotherapy, epoetin can then be considered in accordance with the criteria outlined above for cancer-related anemia.

Epoetin in myelodysplastic syndromes. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematological disorders characterize by ineffective hematopoiesis, and some are considered pre-leukemic diseases. Hematopoietic cytokines and growth factors have become an integral part of the treatment of these disorders. Several small studies had shown that therapy with epoetin increased Hb level and decreased transfusion requirements. In one randomized, double blind, placebo-controlled trial, 87 patients were randomized to receive epoetin or placebo. Significantly, more patients in the epoetin group achieved a hematological response as compared to the placebo group (37% versus 11, p=0.007).[44]

Prediction of response to epoetin alfa. Not all cancer patients respond to epoetin. The reasons for this resistance are unclear, but absolute iron deficiency, or impaired iron utilization and high level of tumor necrosis factor alfa might play a significant role. Patients affected by a concomitant infection may not respond, even with higher doses of epoetin, they should be reconsidered for treatment after the infection subsides. Similarly, patients with rapidly progressive disease and patients undergoing high dose chemotherapy and autologous transplantation respond poorly. Several groups have tried to establish a model to predict response to epoetin. One group, reported that the relationship between the actually observed serum EPO level and the level that can be predicted due to the anemia (observed/predicted EPO level [O/P] ratio) is indicative of a subsequent response to epoetin therapy; levels <0.9 predicted higher response rate whereas O/P ratio over 0.9 were associated with low response rate;[45] however, such determination might not be clinically useful.

Once weekly regimen. There are several limitations in using epoetin; one of which is the requirement for frequent dosing. Two small pharmacokinetic studies suggested that the once weekly dosing, with higher doses of epoetin, achieved similar results compared with the thrice-weekly schedule.[46,47] A large, non-randomized, community-based study, employing once weekly regimen, at a dose of 40,000 IU subcutaneously in 2,964 assessable anemic patients with non-myeloid

malignancies undergoing chemotherapy,[31] has reported similar improvement in Hb level and QOL, compared to those observed in the historical experience with the 3 times weekly dosage schedule.

Recently, a randomized study comparing once weekly epoetin at 40,000 IU, with a placebo control arm, has been reported in abstract form in American Society of Clinical Oncology (ASCO) then updated in American Society of Hematology (ASH) 2002 annual meeting. The final results showed that weekly epoetin injection increased Hb concentration and decreased transfusion requirements, compared to placebo among 344 patients receiving chemotherapy.[48]

Darbepoetin. Experiments on rHuEPO isoforms have demonstrated that the carbohydrate content has significant effect on the in-vivo biological activity of the hormone. Increasing sialic acid content was found to increase serum half-life of rHuEPO.[49,50] Utilizing these ideas, recombinant DNA technology was used to synthesize analogues with an increased sialic acid content; the new molecule was called darbepoetin alfa (Aranesp). Darbepoetin has a similar configuration to rHuEPO, it binds the same EPO receptors as endogenous EPO and rHuEPO, however, compared with rHuEPO, it has a 3-fold longer serum half-life and increased biological activity.[51,52] In a multi-center, double-blind, placebo-controlled study, 320 patients with lung cancer, receiving multicycle platinum-containing chemotherapy regimens, were randomly assigned to receive darbepoetin alfa at a dose of 2.25 mcg/kg subcutaneously or a placebo injection weekly, for 12 weeks. Patients received darbepoetin alfa required fewer transfusions (28% versus 57% $p<0.001$), fewer units of blood (0.67 units versus 1.92 $p<0.001$), had more hematopoietic response (66% versus 24% $p<0.001$), and had better improvement in QOL assessment, using FACT score.[53] Utilizing the several dose-findings studies,[54] a dose of 2.25 mcg/kg subcutaneously, once weekly is recommended. However, due to the dose response relationship, which was demonstrated in several of these studies, it is recommended to double the dose in patient with sub-optimal response (Hb increase <1.0 gm/dL after 4 weeks of therapy). If the Hb response remains inadequate in 4 weeks after dose doubling, then further therapy might not be effective. Increasing the dosing interval of darbepoetin did not appear to be associated with reduction in its efficacy. In patients received darbepoetin at 6.75 mcg/kg once every 3 weeks, 6.75 mcg/kg once every 4 weeks or 10 mcg/kg once every 4 weeks, hematopoietic response rate of 60%, 61% and 70%, was observed, this compared to 10% in the placebo group. When compared to a dose of 2.25 mcg/kg once weekly, darbepoetin at 6.75 mcg/kg once every 3 weeks and 10 mcg/kg once every 4 weeks resulted in a similar rate of hematopoietic response.[55]

What is the optimal hemoglobin level. There is no agreement regarding the Hb level below which rHuEPO should be started. To address this issue, and other uncertainties surrounding the use of epoetin, the ASCO and the ASH, developed an evidence-based clinical guidelines for the use of epoetin in patients with cancer. According to these guidelines, epoetin is recommended for patients with Hb below 10 gm/dL. Use of epoetin for patients with less severe anemia (Hb <12 gm/dL) should be determined by the clinical circumstances.[56] However, a recent retrospective study, published in abstract form at ASH 2002, showed that early administration of epoetin alfa (at Hb >10.5 gm/dL but <12.0 gm/dL) to 251 cancer patients appears to maintain QOL in patients with mild anemia.[57]

Cost issues on blood transfusion versus epoetin. The cost-effectiveness of epoetin was addressed in several studies. A modeling study, drawing cost and effectiveness assumptions from a literature review and from 3 other studies involving more than 4500 cancer patients on chemotherapy or radiotherapy, used what they called quality-adjusted life-years as an end point, the authors concluded that treatment with epoetin can be cost-effective.[58] However, multiple other studies have reached different conclusions,[59,60] with no agreement on the cost effectiveness of epoetin therapy compared with BT. The newer generation of EPO products would probably add to the cost of therapy, however with the added advantage of less frequent dosing. When considering the cost, it is important to emphasize the other advantages, that these products provide over transfusion therapy.

In conclusion, anemia in cancer patients is very common, unfortunately, is often under-recognized and under-treated. Three times a week or once weekly epoetin regimens had shown to significantly increase Hb concentration, along with improvement in QOL and probably tumor response. The recent approval of darbepoetin (Aranesp), adds to the patient's convenience with less frequent dosing (once every 2-4 weeks) with similar efficacy and safety profile as rHuEPO.

Acknowledgment. The author would like to thank Mrs. Esper Anonuevo, Gigi Palado and Wisam Bukhari for their secretarial support in preparing this manuscript.

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