Anaemia and cancer treatment: a conceptual change

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ABSTRACT

Anaemia is the most common haematological abnormality in cancer patients, and unfortunately, it is often under-recognised and undertreated. The aetiopathology of anaemia in cancer patients is complex and is usually multifactorial. There is enough evidence suggesting that tumour hypoxia in anaemic patients has a negative impact on the treatment outcomes in cancer patients. The use of recombinant human erythropoietin is becoming a new standard of care in cancer patients. Various well-controlled studies have shown that the use of erythropoietin (EPO) increases the haemoglobin level, thereby decreasing the need for frequent transfusions and improving the tumour responses, cancer-free survival and quality-of-life parameters in cancer patients. However, a few recent clinical trials failed to replicate the survival benefit. Hence, a free unrestricted use of EPO is to be avoided. The past belief that anaemia does not matter in cancer patients is now considered invalid and is being seriously challenged. This article aims to present some recent findings on the impact of anaemia on outcomes, with discussion on the possible causes and effects. The benefits of the use of EPO analogues in cancer-related anaemia are also presented.

Keywords: anaemia, cancer, cancer-related anaemia, epoetin, erythropoietin, recombinant human erythropoietin

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INTRODUCTION

Anaemia is a frequent complication in cancer, seen in up to 75% patients with malignancies.[1-3] Historically, blood transfusion has been the treatment of choice for severe cancer-related anaemia (haemoglobin [Hb] < 8 g/dL), while mild to moderate anaemia (Hb 8–11 g/dL) was left untreated in most patients. Although blood transfusion is the fastest means to alleviate anaemia-related symptoms, there are both short- and long-term risks associated with it.[4] Further, the development of increasingly more aggressive antineoplastic treatments that may lead to anaemia has increased the need for blood transfusion and prompted a search for other alternative options. Of late, the impact of symptomatic anaemia on a patient's quality of life (QOL) is also a subject of considerable concern.[5,6] The major complaints associated with anaemia are patient fatigue, low energy levels, dyspnoea, dizziness, and associated decrease in functionality.[7]

AETIOPATHOGENESIS OF ANAEMIA IN CANCERS

In patients with malignancies, several factors have been found to be associated with anaemia and its magnitude. These include tumour type,[8,9] disease stage, age of patient, and duration, intensity and type of treatment (chemotherapy/ radiotherapy), along with hypersplenism, blood loss, and nutritional deficiencies. Although some of these factors are either directly related to the tumour or its treatment, in a considerable number of cancer patients, no cause other than the malignant disease itself can be implicated.[10] The term, anaemia of chronic disease, was first used by Cartwright in 1966 when he suggested a conceptual mechanism for anaemia seen in patients with chronic disease. He suggested three mechanisms, which are shortened red cell survival, failure of bone marrow to increase erythropoiesis to meet the demand and to repair the deficiency (i.e. a hypoproliferative state), and failure of the bone marrow to release iron from the senescent red cells phagocytosed by the bone marrow macrophages (i.e. defective iron utilisation).[11]

The anaemia of chronic disease is usually mild with a Hb level of around 9 g/dL, is normochromic or hypochromic in nature, and is associated with a disproportionately low reticulocyte count for the severity of anaemia. The anaemia usually seen in cancer patients is similar, and the same mechanism could easily be applied to the anaemia of malignancy. New evidence suggests that there are abnormalities in the production of erythropoietin (EPO). The hypoproliferative state in cancer-associated anaemia appears to be related to either decreased EPO production or impaired bone marrow response to EPO. Each of these mechanisms leads to the development of the anaemia of malignancy.

The regulation of iron transport by cytokines is a key mechanism in the pathogenesis of anaemia of chronic disease and a promising target for therapeutic intervention.[12] Recent evidence has indicated that

recombinant EPO can correct the anaemia of malignancy in many patients. This has supported the finding of decreased EPO production as an important factor in the cancer-associated anaemia. One concept states that inappropriate secretion of EPO is related to increased cytokine production by the tumour. *In vitro* studies have shown that cytokines, like tumour necrosis factor (TNF) and interleukin-1 (IL-1), inhibit EPO mRNA synthesis. This proves that the hypoproliferative response of the marrow in cancer patients could be a cytokine-mediated phenomenon. Cytokines liberated in cancer patients could cause inhibition of EPO secretion and possibly EPO responsiveness of the marrow erythroid progenitors.

The mechanism of anaemia of chronic disease and anaemia of cancer, as it stands now, is through the liver, the main player being the newly-discovered hormone called "Hepcidin", secreted by the liver cells in response to the action of the inflammatory cytokines from the macrophages and other cells.[13] Hepcidin-dependent iron excretory mechanism through the other hormone called "Ferroportin" is also upset in some situations. Hepcidin in fact blocks the absorption of iron from the intestinal epithelial cells and prevents the recycling of iron by blocking the ferroportin mechanism in the macrophages, which account for a daily turnover of 25 mg of iron for the production of about two billion red cells in the marrow in one day; whereas we absorb only 1–2 mg of iron through our alimentary canal daily.

TUMOUR HYPOXIA

Clinical studies have shown that low haemoglobin levels have a significant impact on treatment outcomes, including survival. The mechanisms by which the treatment efficacy and survival are compromised have not fully been elucidated, but may include cellular compromise (e.g. impaired tumour oxygenation), or more generally, patient compromise (e.g. decreased QOL and treatment delivery). Tumour hypoxia occurs when tumour growth exceeds the ability of local microvasculature to supply oxygen to tumour cells. Several studies have shown that tumours are more hypoxic than the surrounding normal tissue.[14] Tumour oxygenation is mainly affected by the rate of blood flow, microcirculation and Hb concentration; therefore, correcting the Hb level will improve the tumour oxygenation.[15] There is also enough evidence to suggest that, regardless of the treatment, patients with hypoxic tumours are likely to have less local disease control and less cure, compared with patients with better oxygenated tumours of the same size and stage.[16,17]

There are three explanations for the adverse impact of tumour hypoxia on survival. First, hypoxia induces expression of vascular endothelial growth factor (VEGF), which stimulates angiogenesis and increases the potential for tumour growth and metastasis. Second, ionising radiation results in the formation of free radicals within cells. In the presence of oxygen, the free radicals are fixed and interact with DNA and cell membrane to cause cell death. When cells are hypoxic, the free radicals are not fixed and cell death may not occur. Third, hypoxia may produce a growth advantage for tumour cells that are resistant to apoptosis, with a decrease in potential for cure or control.[18]

EFFECT OF HYPOXIA ON TREATMENT OUTCOMES

The impact of anaemia on radiotherapy has been well investigated. In a retrospective study of 889 patients of head and neck tumours treated with radiotherapy, long-term outcomes were evaluated.[19] The estimated five-year survival rate for patients with Hb ≥ 13.0 g/dL for males and ≥ 12 g/dL for females was 58.2%, compared with 28.4% for patients with Hb levels below these respective values (p < 0.0001). Similar findings of significant differences in survival, as well as local disease control and distant metastasis, have been reported by various other investigators.[20,21] The overall conclusion from these studies is that the critical haemoglobin level is the level achieved or maintained during radiotherapy, not the baseline level.

There is also evidence to suggest an adverse effect of anaemia on the response of tumour cells to chemotherapy. Factors that may give rise to intrinsic or acquired resistance include inadequate tumour vascularity, tumour hypoxia,[22] proportion of cells in cycle, and genetic changes in the tumour cells such as overexpression of multidrug resistance phenotype or overexpression of p53.[23] Evidence from laboratory studies has also suggested that hypoxic cells are two- to six-fold more chemoresistant to cytotoxic drugs than normoxic tumour cells.[24] The clinical significance of these findings is becoming clearer from the recent data of cervical and uterine cancer patients, which strongly supports the concept of hypoxia-induced selection of cells that are resistant to apoptosis as the mechanism of malignant progression.[18]

TREATMENT OF ANAEMIA AND ITS IMPACT ON CANCER TREATMENT OUTCOMES

Traditionally, the assessment of cancer-related anaemia is based primarily on the quantitative measurement of haematocrit or Hb, with considerable less emphasis on the patient's symptoms and changes in functional status and QOL. Also, instead of following the patient's symptoms and quantitative measurements over time to establish trends, considerable reliance is placed on a

single measurement. There are several multidimensional questionnaires available for use to investigate these factors in clinical use; e.g. Piper fatigue scale, functional assessment of cancer therapy general (FACT-G a 33-item scale), FACT-F (FACT-G with 13 additional items), FACT-An (FACT- F plus seven additional items). Blood transfusion has been a common approach to correct anaemia in cancer patients. Unfortunately, blood transfusions carry significant risks of transfusion reactions, iron overload and reduced immunocompetence induced by foreign proteins. Further, more blood transfusions will result in an immediate rise in Hb level, but the level will fall again unless transfusion is repeated.

A recombinant human EPO (epoetin) is now available for treatment of anaemia associated with cancer and cancer treatment. The results of a comprehensive review of the existing literature guided the development of joint recommendations for the treatment of cancer-related anaemia by the American Society of Clinical Oncology (ASCO) and the American Society of Hematology. These consensus guidelines have helped to define and optimise the treatment of anaemia in cancer with epoetin.[25] The use of epoetin in patients receiving chemotherapy has been shown to increase Hb level and improve the patient's sense of wellbeing in many controlled trials.[26,27] It has also been effectively shown to increase the Hb level in patients receiving radiotherapy,[28,29] and in patients receiving combined chemoradiotherapy.[30,31] The effect of epoetin with radiotherapy on the rate of recurrence in patients with pelvic malignancies has been shown in a study of 385 patients. In this group, 190 patients received epoetin with iron supplement and 195 patients received only iron supplement.[29] The mean Hb level for patients who received epoetin plus iron was 12.9 g/dL, vs. 10.6 g/dL for patients who received only iron (p = 0.007). There was a significantly lower rate of disease recurrence in patients who received epoetin (22/19; 11.6%), compared with the other group who received only iron (44/195; 22.6%) (p = 0.007). These results suggested that epoetin is effective in decreasing the risk of recurrence in patients with pelvic malignancies receiving radiotherapy.

Another large placebo-controlled trial of 375 anaemic patients was conducted to assess the effect the of epoetin on transfusion requirements, Hb level, QOL and safety, compared with a placebo.[26] Patients who were treated with epoetin had a significantly decreased transfusion requirement (p = 0.0057), increased Hb concentration (p < 0.001) and improved QOL (p < 0.05). Median survival for the epoetin group was 17 months, as compared to 11 months for the placebo group.[32] Similar favourable results were shown in an Austrian study of 60 patients with head and neck cancer treated with chemoradiotherapy,[28] which showed that treatment with epoetin (n = 30) increased

Hb level, decreased transfusion requirement, and also significantly improved the response rate (p = 0.009), local control (p = 0.03) and two-year overall survival (p ≥ 0.03).[28] Another recent meta-analysis involving 57 trials and including more than 9,000 patients had also arrived at a similar conclusion, that the treatment with epoetin or darbepoetin significantly reduced the risks of red cell transfusion (relative risk [RR] 0.64, 95% confidence interval [CI] 0.6–0.68; over 42 trials and > 4,300 patients). However, caution is advised in using the epoetin analogue therapy in patients receiving a combination of thrombogenic chemotherapy agents or those at high risk for them in view of the increased risk of thromboembolic events associated with treatment (RR 1.67, 95% CI 1.35–2.06; over 35 trials and > 6,700 patients).[33]

The overall evidence on the influence of EPO on survival of cancer patients is still not certain. In a systemic review of 60 articles reporting the survival of cancer patients in relation to anaemia and Hb concentration, Caro et al reported a 65% increase in the RR of death for anaemic cancer patients.[34] Similar findings have been previously reported by Binet et al in chronic lymphocytic leukaemia patients.[35] Anaemia at the time of diagnosis has been reported as an independent adverse prognostic factor in patients with Hodgkin's[36] and non-Hodgkin's lymphoma (NHL).[37] However, two recent randomised-controlled trials looking at survival benefits due to a higher Hb achieved with EPO analogue, demonstrated reduced survival in the treatment arm receiving epoetin. The first of these by Henke et al looked at 351 head and neck cancer patients undergoing radiotherapy and receiving epoetin or a placebo to maintain Hb levels > 14 g/dL in females and > 15 g/dL in males. The overall survival was lower in the treatment arm compared to that in the placebo arm (RR of death 1.39, 95% CI 1.05–1.84, p = 0.02). The treatment arm had more episodes of hypertension, haemorrhage and thromboembolic events compared to the placebo arm (11% vs. 5%), more patients died of cardiovascular causes in the treatment arm (5.5% vs. 3%) and the locoregional tumour progression was also higher in the treatment arm (RR 1.69, 95% CI 1.16–2.47, p = 0.007) compared to the placebo arm of the trial.[38]

The second study by Leyland-Jones et al involved 939 patients with metastatic breast cancer, randomised to receive epoetin or a placebo. The study was prematurely terminated, based on the results of four months of safety data (41 deaths in the treatment arm against 16 in the placebo arm). The survival was significantly less in the treatment arm at the one-year review (70% vs. 76%, p = 0.01). However, the survival curve of the two arms converged at the 19-month follow-up. Again, this difference was more due to higher thromboembolic events (1.1% vs. 0.2%) and disease progression (6% vs. 2%).[39]

The adverse findings of these two studies have been hypothesised to be due to methodological and biological factors relating to thromboembolic complications and stimulation of tumour growth by EPO. It has been proposed that relief of tumour hypoxia may promote its growth, and the expression of EPO receptors on breast cancer, head and neck cancer cells,[40] and in other cancers indicate this. However, this observation is not expressed across all trials.[41] Further, there is no justification at present for routine testing of EPO receptor before initiating epoetin therapy in a cancer patient with anaemia. Darbepoietin alpha, a newer erythropoietic agent, has an extended half-life compared with epoetin alpha and epoetin beta, as well as increased biological activity allowing for less frequent dosing.[42]

More recent research with epoetin has focused on the identification of the variables that are predictive of future response to the therapy. These include the baseline variables, such as serum ferritin, serum EPO levels, and baseline Hb levels, as well as the early response variables.[43-46] However, results have yet to demonstrate clinical sensitivity and specificity in prognosticating the response to epoetin.[47] Although recent studies have shown that treatment of mildly anaemic patients (baseline Hb 10–12 g/dL) with epoetin results in a better response compared to those patients whose Hb is allowed to drift down,[21,32] there still remains a compelling need to increase awareness of cancer-related anaemia, as well as to understand the consequences of its suboptimal treatment.

When QOL of previously-transfused patients was compared with transfusion-naïve patients with comparable levels of Hb via FACT-An and LASA, the results showed a poorer QOL for transfused patients, suggesting that raising Hb levels by transfusion of red cells may not provide the same functional capacity for patients as their own *de novo* Hb increase through epoetin. Further existing evidence indicates that cancer patients who received transfusion prior to epoetin are at a higher risk of additional transfusions compared to those who are transfusion naïve. Early administration of epoetin to prevent a drop in Hb levels can thus reduce the risk of future transfusions. The issue of the use of epoetin for managing anaemia in cancer patients is well addressed in the ASCO guidelines[25] on this matter. In view of recent concerns regarding the adverse events associated with the use of epoetin in cancer patients, it is prudent to restrict the use of EPO analogues to cancers associated with chemotherapy with Hb < 10 g/dL. Other patients with a continuing decline in Hb but not yet reaching this level will need a treatment that is individualised.

The recommended dose of epoetin is 150 units/kg of body weight administered thrice a week for four weeks, with a consideration to double the dose for another 4–8 weeks in patients with a poor response. Alternatively, a single weekly dose of 40,000 units may also be considered with a similar escalation of dosage. The therapy should be targeted to achieve and maintain a Hb level of 12 g/dL. In the absence of an adequate response (rise in Hb level < 1–2 g/dL) despite treatment for 4–6 weeks, consideration should be given to terminating the treatment and looking for other causes of anaemia and disease progression.

CONCLUSION

The view that anaemia associated with cancer is to be expected and that the anaemia does not cause the patient any immediate serious harm until the Hb level falls below 10.0 g/dL or even < 8 g/dL is invalid now. Increasing evidence suggests that anaemia adversely affects both the survival and the functional capacity and QOL parameters of cancer patients. While the current data is insufficient to confirm the direct survival benefit of epoetin treatment, improving patients' QOL may result in an enhanced survival by indirect effects. Treatment with epoetin by increasing Hb may not only permit more aggressive newer antineoplastic treatment to be completed on schedule, but may also decrease tumour hypoxia with a probable decrease in the malignant potential of the tumour and possible increased sensitivity to the cytotoxic chemotherapy. Treatment with epoetin, by improving the patient's QOL (secondary to raised Hb), may allow the patients to receive the correct treatment doses of chemotherapy in a more timely fashion than patients who remain anaemic. However, a few recent clinical trials failed to reveal the expected survival benefit and rather showed an adverse outcome. Hence, until more definitive evidence is generated, epoetin therapy should be used for patients with cancer-associated anaemia, targeting an Hb level of 12 g/dL. Finally, the old (and at times, current) notion that anaemia does not matter in cancer patients is being seriously challenged.

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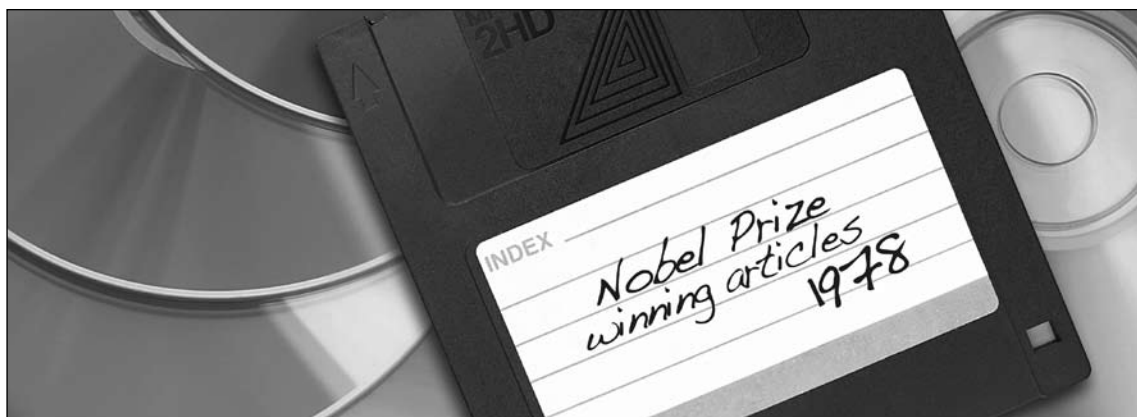
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