

The Impact of Darbepoetin Administration in Haemoglobin Levels and Quality of Life in Cancer Patients Undergoing Radiation Treatment

a report by

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Dr Antonadou is a member of several national and international societies including the American Society of Therapeutic Radiology and Oncology and the American Society of Clinical Oncology. She has given lectures in radiation induced toxicities, combined treatment, chemoradiation in head and neck cancer, lung cancer and others. Dr Antonadou has over 120 publications to her credit and is a reviewer in many journals.

Her research interests focus on the prevention of adverse events induced by radiotherapy or radiochemotherapy combined modality treatment for various tumour types; quality of life, supportive care, brain tumours and brain metastases, as well as organ preservation. Dr Antonadou received her BSc degree in physics, and trained in medical physics at Curie Hospital in Montpellier, France and at the Royal Marsden Hospital, London. After this she continued her studies at Athens University and became a medical doctor in 1982. After her residency training in radiation oncology she was board certified in Athens as radiation oncologist.

Cancer is frequently associated with significant anaemia, either as a result of the disease itself or the effects of cancer treatment, particularly cytotoxic chemotherapy, radiation treatment or concurrent administration of both. The prevalence of anaemia varies according to the type of tumour. About 50% of patients with solid tumours present with anaemia at diagnosis. It is defined as an inadequate circulating level of haemoglobin or red blood cells. The pathophysiology of tumour-related anaemia is multifactorial. Tumour-associated factors such as tumour bleeding, haemolysis and deficiency in folic acid and vitamin B12 can be acute or chronic.

Treatment-associated factors may aggravate the incidence of anaemia and they may compromise patient's tolerance of treatments, resulting in the need to reduce the duration or intensity of those treatments. Dose-intensified regimens and combined modality schedules of chemotherapy and intensified radiotherapy result in a higher degree of anaemia. The increase in the total radiation dose administered with the new radiotherapy techniques, such as conformal or intensified modulated radiation treatment (IMRT), combined with the newer chemotherapeutic agents, such as taxanes, which are strongly myelosuppressive, are possibly responsible for the increased incidence of anaemia and might require treatment interruptions, which compromise efficacy.

The clinical manifestation and severity of anaemia vary considerably among individual patients and is associated with its own set of debilitating signs and symptoms it can have a significant effect on morbidity and mortality, as well as on the level of care that patients require. Chronic anaemia can result in severe organ damage affecting the cardiovascular system, immune system, lungs, kidneys and the central nervous system. In addition to physical symptoms, the subjective impact of cancer-related anaemia on quality of life (QoL), mental health and social activities may be substantial. A common anaemia-related problem is fatigue, which impairs the patient's ability to perform normal daily activities.

Tumour Hypoxia and Anaemia, the Impact on Treatment Efficacy

Another aspect of anaemia in patients with malignant disease is the effect on the tumour itself, and in several cancers such as cervical carcinoma, head and neck cancer, prostate and lung cancer it is associated with poor prognosis. Hypoxia is a characteristic pathophysiological property of solid tumours that occurs across a wide range of experimental and human malignancies. Hypoxic regions have been identified in locally advanced breast and cervical tumours, head and neck cancer, prostate cancer, pancreatic cancer, rectal cancer, brain tumours, soft tissue sarcoma and malignant melanoma. Tumour hypoxia, acting through direct or indirect mechanisms, or both, may contribute to resistance to radiotherapy, some chemotherapy regimens and chemo-radiation which can lead to a poorer clinical outcome.

Tumour cells can become resistant to cancer treatments because of hypoxia; this is due to decreased oxygen transport capacity as a result of tumour-associated anaemia, which can contribute to the development of hypoxia. Owing to an abnormal microenvironment, solid tumour tissue is often hypoxic. Hypoxia may be more prevalent in anaemic patients than in patients with normal haemoglobin (Hb) levels.

Results from both prospective and retrospective studies in patients with various tumours undergoing radiation treatment or combined modality therapy have indicated that anaemia may be associated with decreased overall survival and reduced locoregional control. In a cervical cancer study, increased hypoxia was associated with decreased local control and lower rates of disease-free survival and overall survival. In a number of retrospective studies, the adverse relationship between pre-treatment haemoglobin levels and locoregional tumour control has been shown in patients with early-stage glottic cancer treated by radiotherapy alone. In a study by Warde et al., 735 patients with T1/T2 glottic cancer were treated by radiotherapy alone and the pre-

treatment haemoglobin level was found to be an independent prognostic factor for locoregional control. In another study, Overgaard et al. were among the first investigators to observe a correlation between locoregional tumour control and haemoglobin concentration. In the Danish study an important correlation was found between locoregional control and Hb concentration for supraglottic and pharyngeal tumours. The increased tumour control reflected the extent of improvement predicted by the oxygen enhancement ratio. These observations generated the hypothesis that strategies to diminish cancer-related anaemia might not only relieve patients from anaemia related symptoms, but could also improve tumour response and possibly overall survival.

(ESP). The American Society of Hematology/American Society of Clinical Oncology guidelines recommend starting anaemia treatment with ESP when haemoglobin levels decline to less than 10g/dL. The guidelines are based on the results of trials published between 1985 and 1999.

Human erythropoietin is an acidic glycoprotein hormone and the primary regulator of human erythropoiesis. This hormone is mainly synthesised in the kidney and to a minor degree in the liver. Tissue hypoxia triggers the synthesis and releases erythropoietin into the blood plasma. Erythropoietin has two major functions; stimulating the erythroid progenitor cells and maintaining their viability.

Cancer is frequently associated with significant anaemia, either as a result of the disease itself or the effects of cancer treatment.

Anaemia Management

Before 1993, when recombinant human erythropoietin (rHuEPO) was approved by the US Food and Drug Administration (FDA), red blood cell (RBC) transfusion was the only option for the treatment of anaemia in cancer. The availability of a therapeutic option with an apparently superior risk/benefit ratio has changed clinical practice and resulted in an increased understanding of the impact of anaemia treatment in cancer patients. RBC transfusion can improve patient QoL by relieving symptoms caused by anaemia. Potential complications associated with blood transfusion are: transmission of infectious diseases, transfusion reactions and immune modulation with possible adverse effects in tumour growth.

Optimal transfusion thresholds have been discussed in the literature. The British Society for Haematology recommends that mild anaemia be left untreated. RBC transfusions are indicated for patients with Hb levels below 7g/dL. There no clear recommendation for Hb levels between 7 and 10g/dL. Following these guidelines, RBC transfusions are rarely needed for patients with Hb levels higher than 10g/dl. As a consequence, the perception developed that mild to moderate anaemia was not clinically important in these patients. However, data have emerged demonstrating that this was false, and that treatment efficacy and QoL can be substantially improved by treatment with erythropoiesis-stimulating proteins

Darbepoetin alpha is a second-generation erythropoietic protein created through site-directed mutagenesis of the human erythropoietin gene to provide two additional glycosylation sites and permit increased amounts of post-translational glycosylation. As greater degrees of glycosylation are associated with increased *in vivo* potency through prolonged serum half-life, darbepoetin alpha can be administered every three weeks without compromising efficacy in the cancer patient. Guidance for the use of darbepoetin alpha was given in recently published guidelines of the European Organisation for Research and Treatment of Cancer.

Comparing the different guidelines, ESP treatment is generally recommended in anaemic non-myeloid cancer patients undergoing chemotherapy who have an Hb of less than 10g/dL. ESP can also be given in patients with Hb levels of 10-12g/dL depending on clinical circumstances or risk factors for developing anaemia.

Efficacy of ESP Administration in Haemoglobin Response

The ability of ESP to increase Hb levels and reduce the risk for blood transfusions in cancer patients has been demonstrated in several randomised controlled trials and meta-analyses. A large number of additional controlled clinical trials have been performed and were reviewed in a meta-analysis. The general consensus reached by this meta-analysis was that

rHuEPO reduced the odds of transfusion in patients receiving chemotherapy or radiotherapy.

Darbepoetin was introduced in 2003, and two large trials in patients with lung cancer and malignant lymphoma have been reported. In a double-blind placebo-controlled phase III study in 320 small cell lung cancer patients undergoing platinum-based chemotherapy, darbepoetin was given at a dose of 2.25 µg/kg per week, for 12 weeks. At baseline patients had a median Hb level of 10g/dL. Significantly fewer patients received transfusions in the darbepoetin arm than in the placebo arm (27% versus 52%).

In a prospective multicentre open label study the efficacy and safety of darbepoetin administration, as well as the impact on QoL, were evaluated in cancer patients undergoing conventional radiation treatment. Patients were eligible for this study if they were older

haemoglobin level at baseline was 10.95 ± 1.76 and during week 10 the Hb level was 12.96 ± 2.33 . There was a significant increase in mean Hb levels from the second week onwards with the peak value at week 10 from the baseline (17.1% increase) and remaining so two months after the end of the radiation treatment with Hb level 12.61 ± 2.15 . This Hb level was still significantly higher compared with the baseline level. Another important issue is that transfusion requirements were minimal in this cohort of patients, transfusion following the protocol was allowed in patients with Hb level $\# 9\text{g/dL}$, and only three (3%) of the patients required a red blood transfusion.

None of the patients experienced any adverse events. Darbepoetin administration was well tolerated. Safety was assessed through adverse event reporting and the monitoring of vital signs and laboratory parameters.

The subjective impact of cancer-related anaemia on quality of life (QoL) may be substantial.

than 18 years, with a pathologically confirmed solid tumour, a good performance status (Eastern Cooperative Oncology Group <2), with life expectancy of at least six months, and they had to provide informed consent. The patients were scheduled to receive conventional radiation treatment. Patients with uncontrolled hypertension, with bleeding or haemolysis and those who had received transfusion within 12 weeks before the start of radiotherapy were excluded from the study. All patients underwent conventional external beam radiation treatment with 2Gy daily dose, five days per week to a total dose of 50-60Gy; 150mcg darbepoetin was administered once per week during radiation treatment. All patients received iron supplementation.

Between March 2002 and February 2004, 140 patients were entered in this study; 116 were evaluable. The mean age of the patients was 72.8 ± 17.8 , and they were 54 male and 62 female. The primary tumour site was breast in 26% of patients (30), lung cancer in 17.4% (20 patients), pelvic tumours in 38.3% (44 patients), head and neck tumours in 9.5% (11 patients) and the remaining in various tumour sites. The majority of the patients had ECOG performance status 0.38% (48 patients) and 1.37% (43 patients).

All patients were monitored weekly and haemoglobin levels were measured. The mean

Changes in Health-related QoL Parameters

In recent years, improvements in cancer care have also focused on patient QoL. The adverse effects of anaemia affect every patient diagnosed with a malignant condition by causing fatigue and thus impairing the patient's QoL. Community studies evaluated the relationship between Hb level and QoL parameters in cancer chemotherapy patients. All these trials documented significant improvements in energy, activity and overall QoL, associated with a significant increase in Hb level. An increase in haemoglobin consequent to treatment was associated with an improvement in QoL score for the range of 8-14g/dL. The most substantial improvement in QoL scores occurred when the haemoglobin level increased from 11g/dL to 12g/dL.

In another study Littlewood et al. investigated the effects of epoetin alpha on QoL in a placebo-controlled trial. Statistically significant improvements measured by the QoL scales were found in all three cancer-specific QoL scales for patients receiving epoetin alpha compared with placebo. The overall QoL was significantly improved in patients receiving epoetin alpha compared with controls ($p=0.0048$).

The only trial that evaluated QoL outcomes in cancer

patients undergoing radiation treatment is the one conducted by the Hellenic Group for Clinical Radiation Oncology. This was not a randomised study and all cancer patients received 150mg of darbepoetin during radiation treatment. The effect of darbepoetin alfa on patient QoL was a major component of this study and was assessed with validated instruments such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire. The FACT-An questionnaire QoL evaluation was completed by the patients at baseline, six weeks (end of radiation treatment) and two months after radiation treatment RT). Response to RT is usually evaluated at two months after the end of the treatment. QoL is a subjective multidimensional concept that includes functional activity and emotional and social wellbeing as influenced by disease and treatment side effects. Patients with lower Hb levels had lower scores and therefore reduced QoL compared with patients with higher Hb levels. There was a significant difference in physical wellbeing score between Hb levels ($p=0.016$) regardless of the time of point measurement. Patients with high Hb levels had significantly higher functional wellbeing scores regardless of the time of measurement ($p=0.002$). At the same time there was also a significant difference in mean fatigue score between Hb levels ($p=0.019$), as well as a significant time by group interaction

($p=0.03$). Patients with higher Hb levels are showing improvement in terms of fatigue over time. In this study, where patients received darbepoetin during radiation treatment, the Hb levels were increased significantly from baseline during the RT period, irrespective of tumour localisation, stage of the disease age and gender, and they reached the maximum value at week 10 from baseline and remained so two months after the end of the treatment. Increased Hb levels were associated with better social and functional performance, as well as reduced fatigue.

Conclusions

Anaemia is common in cancer patients undergoing chemotherapy or radiotherapy. ESP may be used routinely outside clinical trials to increase Hb and reduce the need for transfusion in patients with Hb less than 9g/dL. The administration of ESP improves QoL in patients undergoing radiation treatment and reduces transfusion requirements, and, at the same time, allows the patients to complete radiation treatment without interruptions which might compromise treatment efficacy. ■

A longer version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchoncologicaldisease.com).

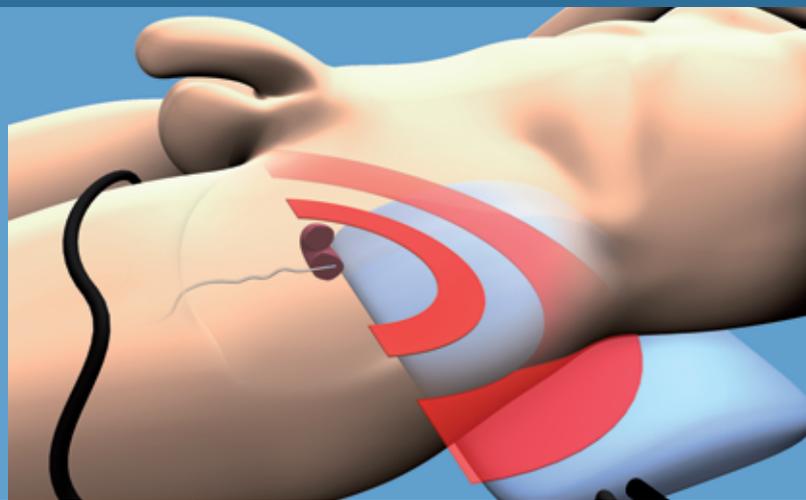
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