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Does caring fatigue improve survival?

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Venice, Italy

May 15-18, 2003

GUEST EDITOR: TEODORO CHISESI

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Foreword

T. Chisesi

Over the last ten years, the introduction of new treatments for cancer has transformed the management of the patient with cancer into that of the patient with a chronic disease.

This enormous progress has focused increasing attention on the quality of life of patients, who although still having to live with their disease, find they have a longer life expectancy. The improved prognosis is such that nowadays patients with cancer continue their daily activities, employment and social life.

Thus, although research must strive to reach the final goal of curing the cancer, in daily clinical practice solutions must be found to all the cancer patient's requirements. It goes without saying that the patient with cancer wants to be cured, but he or she also wants to be able to live with the disease in such a way that the difference between the time before and after the diagnosis is as unobtrusive as possible.

Clinical research over the last few years has considered, identified, and begun to understand the causes of a poor quality of life in patients with cancer and treatments to improve this. The role of anemia is particularly under the spotlight of clinical research. In fact, anemia is always a sign of disease and, in many cases, is associated with a worse evolution of the disease itself.

The articles in this supplement are intended to quantify the incidence and importance of fatigue in the management of the patient with cancer.

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Anemia in hematologic malignancies: causes, consequences and evidence for treatment recommendations

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Anemia is a frequent finding in patients with hematologic malignancies. In multiple myeloma (MM), the incidence of chronic anemia of variable severity has been reported to range from 21 to 77%. Anemia is one of the diagnostic criteria for MM,[1,2] and it can be severe (Hb < 8 g/dL) in about 10-20% of patients[2,3] who are unresponsive to chemotherapy, in relapsed or advanced disease phase (Table 1).

Its origin is multifactorial, with the most common type being anemia of chronic disorders. The suppressive effect of pro-inflammatory cytokines produced by malignant plasma cells seems to play a pivotal role in the pathogenesis of anemia.[4] Recent studies, carried out by our group, have demonstrated another pathogenetic mechanism of anemia in MM, namely excessive erythroblast apoptosis promoted by myeloma cells.[4] The pathophysiologic consequences of anemia depend on many factors, including its degree, the rapidity of its onset, and the patient's clinical features. Anemia markedly decreases patients' overall quality of life (QoL) and sense of well-being. Fatigue, emotional disturbances and decreased cognitive function are the most prevalent symptoms affecting QoL.[6]

In addition, different hypotheses have been formulated to explain the observation that anemia is a negative prognostic factor for survival in cancer patients, including those with hematologic malignancies.[7] Anemia may have an effect on the chemotherapeutic agents, which require a certain level of oxygenation for optimal activity.[8] As recently demonstrated, red blood cells, as an important transport system,

Study	Anemia definition	% Anemic pts
Kyle (1975)	Hb<12g/dl	62%
Steurer (2001)	Hb<12g/dl	77%
Beguin (1992)	HCT < 45%	>50%
San Miguel (1995)	Hb < 10.5 g/dl	68%
Maclennan (1994)	Hb <10 g/dl	45%
Durie (1975)	Hb < 8.5 g/dl	21%

Ludwig H et al. Hematol J. 3: 121-130, 2002

Table 1. Anemia prevalence in MM at diagnosis.

play a critical role in the delivery of cytostatic agents (anthracyclines and ifosfamide) to the tumor cells.[8,9] Another survival-related effect of anemia may be due to its negative impact on patient's QoL, which could indirectly reduce the patient's compliance to chemotherapy.[10] The question of whether treatment of anemia itself can affect survival is currently under investigation.

In the past, blood transfusion, with its inherent risk profile (infection, transfusion reactions, etc.), was the foundation of hematologic support. The present availability of recombinant human erythropoietin (epoetin) with a far different risk-benefit ratio has changed clinical practice. Numerous studies have confirmed the relationship between anemia, fatigue and other anemia-related symptoms, and correction in QoL following improvement of anemia.[11-14] A direct relationship exists between Hb increase during epoetin α therapy and corresponding

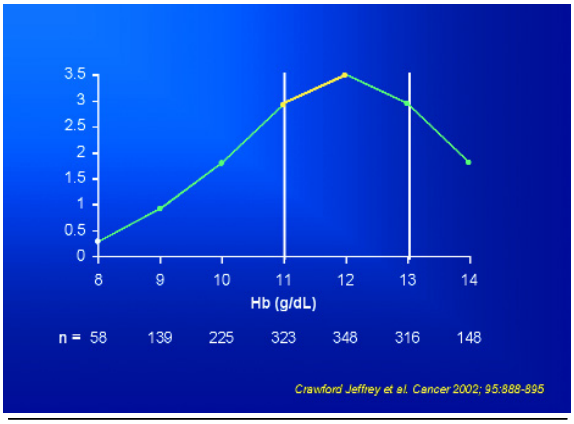

Figure 1. Incremental change in QOL and Hb levels.

QoL improvements in cancer patients, with the maximum QoL gain occurring at a Hb level of 12 g/dL[15] (Figure 1). The efficacy and safety of epoetin in treating anemia has been well demonstrated by a large number of studies.[11-14]

The *American Society of Clinical Oncology* (ASCO) and the *American Society of Hematology* (ASH) established a panel to develop evidence-based guidelines on the use of epoetin in patients with cancer, simultaneously published in Blood and the Journal of Clinical Oncology.

The *Blue Cross and Blue Shield Associations Technology Evaluation Center* (TEC) reviewed 22 controlled trials (18 with epoetin α and 4 with epoetin β) that enrolled a total of 1927 patients.[16] Of the 22 trials, 18 were randomized, 7 of which were placebo-controlled and double-blinded. Because of the varied nature of methodological rigor used in these studies, the TEC report used 3 criteria to label studies of *higher quality*: (i) randomized, controlled trials; (ii) double blinding; and (iii) low attrition (ie, fewer than 10% patients excluded from analysis).

Prior to discussing their specific recommendations (Table 2) on the use of epoetin, the ASH/ASCO guidelines recommend evaluating the cause of anemia in all cancer patients. While chemotherapy or underlying hematologic malignancy can certainly cause anemia, they recommend ruling out other causes of anemia prior to proceeding to therapy with stimulants of erythropoiesis.

Intriguing preclinical and clinical data seem

Table 2. Summary of ASCO/ASH recommendations.

1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level ≤ 10 g/dL. RBC transfusion is also an option depending upon the severity of anemia or clinical circumstances
2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration < 12 g/dL, but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions
3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice-weekly regimens
4. Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.
5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.
6. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring
7. There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.
8. Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.

to suggest that the benefits of epoetin treatment are not limited to the correction of anemia and QoL improvements in MM. In a murine model of myeloma, Mittelman *et al.*[17] demonstrated that epoetin α induced complete tumor regression in 30 to 60% of animals. The use of epoetin α was also associated with a reduction in the serum M-component. These findings were accompanied by a prolonged survival rate.[18] In addition, evidence from clinical trials showed that epoetin α administration may have a survival benefit in patients with solid or hematologic malignancies. Littlewood's study,[10] although it was not designed or powered to study survival, showed that the 12-month survival estimate was 60% for the epoetin α-treated group compared with 49% for the placebo group; mean survival time was 17 months versus 11 months, respectively.

In summary, the occurence of anemia in patients with MM is of growing concern, as there is increasing clinical evidence indicating that anemia and its sequelae can negatively affect patients' QoL, treatment outcome, and long-term prognosis. Therefore, epoetin should be considered an important treatment for the overall management of anemic patients with hematologic malignancies.[19]

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Correlation Between Fatigue and Hemoglobin Level in Multiple Myeloma Patients: Results of a Cross-Sectional Study

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Anemia is the most common finding in hematologic malignancies.[1] In multiple myeloma (MM) about 60% of the patients have a hemoglobin (Hb) concentration ≤12 g/dL.[2] Other studies reported that approximately 50% of MM patients have a Hb < 10 g/dL.[3,4] Mild to moderate anemia, with Hb levels between 8 and 12 g/dL, results in symptoms of asthenia, loss of strength and energy, with a negative impact on patients' quality of life (QOL).[5,6]

The objective of this cross-sectional study was to examine the relations between QOL, Hb level, and other characteristics in patients affected by MM.

This large-scale, cross-sectional study was conducted in 24 Italian centers between November 2001 and March 2002. An anemia-specific QOL questionnaire with a fatigue subscale was used to assess the impact of this symptom on patients' QOL. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire, designed to measure anemia-related and general QOL in cancer patients, includes 20 anemia-specific items: 13 items comprising a fatigue subscale and 7 non-fatigue items. A part of the Functional Assessment of Chronic Illness Therapy (FACIT), the FACT-An reliably discriminates among Hb levels and has been validated and used extensively in cancer studies.[7] The anemia subscale scores range from 0 to 80, lower score indicating poorer QOL.[7]

The characteristics examined included gender, age, disease duration, response phase, Durie and Salmon stage, previous/concomitant cancer therapy, transfusion dependence, and use of recombinant human erythropoetin (rHuEpo, epoetin).

Hb values ranged from 6.4 to 11.8 g/dL in transfusion-dependent patients, and from 7.6 to 17.0 g/dL in transfusion-independent patients; 51% of the population of patients had a Hb value ≤ 12 g/dL.

This cross-sectional Italian study found FACT-An scores to be directly related to Hb level, with mean scores increasing from 48.4 for patients with a Hb of 10 g/dL to 59.6 for those with a Hb of >13 g/dL (Figure 1).

A stronger correlation with Hb level was observed for the FACT-An fatigue subscale than for the non-fatigue items (r = 0.277, p = 0.0001 vs r = 0.214, p=0.001). Significant differences in Hb level were related to gender, can-

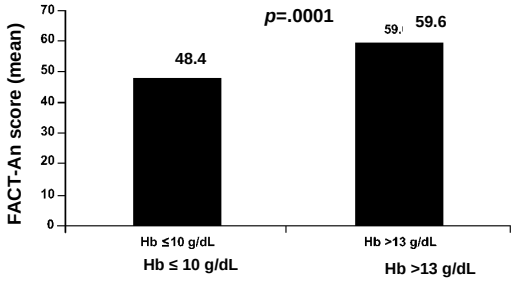

Figure 1. Correlation between FACT-An scores and Hb levels (r = 0.279): lower Hb levels are reflected in lower FACT-An scores indicating a negative impact on QOL.

cer treatment response, staging, and concurrent chemotherapy. Analysis of covariance showed that this relationship was not explained by the effect of covariates.

Hemoglobin levels have the greatest predictive value for a patient's QOL.

Anemia treatment to a Hb level of >12 g/dL should be considered an integral part of the global management of patients with MM, with the goal of reducing the impact of fatigue and improving overall QOL.

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Impact of Fatigue in Lymphoma Patients: Preliminary Results of the Italian Survey on Lymphoma

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Lymphomas are a group of diseases that share a common cell of origin and a particular mode of development. They consist of numerous subgroups, some of which can be cured, such as Hodgkin's lymphoma.[1] Cure and remission are the aim of initial therapy and can be achieved in about 50-60% of patients with non-Hodgkin's lymphoma.[2] However, some patients cannot be offered regimens consistent with such strategies. Instead, these patients require palliative treatment, either at the time of diagnosis due to advanced age or to concomitant incapacitating conditions, or at a later stage following unsuccessful curative treatment. Such patients should be treated only for symptoms impairing their quality of life, for the remainder of their life expectancy. For those patients in whom cure is achievable, more intense strategies are employed with the potential for greater toxicity and associated negative impact on quality of life. Patients with hematologic malignancies often have anemia as this is frequently related to the disease, its treatment, or a combination of these effects.[3] The reported prevalence of anemia, among patients with non-Hodgkin's lymphoma, is 42% at diagnosis and about 65% to 72% during chemotherapy.[3] For patients with Hodgkin's disease, reported prevalence rates are 45% at diagnosis, and up to 72% during chemotherapy.[3] An accumulating body of evidence suggests that anemia may also be a negative prognostic factor in non-Hodgkin's lymphoma and Hodgkins' lymphoma patients.[4-6] Anemia also predicts treatment response in patients with mantle cell lymphoma[7,8] and second-line response in acute myelogenous leukemia.[9] In previously treated chronic lymphocytic leukemia patients, Hb was prognostic for survival and predictive for treatment response.[10] In addition, anemia has detrimental effects on quality of life (QOL).[11] Fatigue is the primary symptom that adversely affects the QOL and it is the most disturbing physical problem reported by cancer patients. Clinical trial results have demonstrated significant improvements in QOL, measured with different measurement tools, in cancer patients subsequent to their hemoglobin level being increasing with epoetin. Studies by Glaspy *et al.*,[12] Demetri *et al.*,[13] and Gabrilove *et al.*,[14] investigating the use of epoetin for the treatment of cancer-related anemia, reported significant increases in quality of life, energy level, and activity level in patients who achieved an increase in Hb level. Similar results were confirmed in the double-blind study published by Littlewood *et al.*[15] Anemia may have detrimental effects on survival through its effects on quality of life, although the mechanism of this association has yet to be determined. It was suggested that a low QOL score might diminish the patient's ability to combat the disease or lower his/her motivation to continue the anti-cancer treatments. A retrospective study of 474 patients with solid or hematologic malignancies examined the effect of QOL on survival. A high global QOL score was significantly correlated with increased survival ($p<0.001$) but was independent of other prognostic factors such as tumor type, extent of disease and performance status. In addition, global QOL score may be considered as an independent prognostic variable for survival in cancer patients receiving chemotherapy.[16]

On the basis of these observations, a prospective survey is being carried out to assess the impact, the prevalence and the consequences of fatigue in lymphoma patients during their chemotherapy treatment. QOL was assessed using the Functional Assessment of Cancer Therapy - Anemia (FACT-An)[17] questionnaire at baseline and at the end of the chemotherapy cycle. This patient-administered questionnaire includes 20 items, 13 fatigue-related items comprising the FACT-An fatigue subscale and 7 non-fatigue related items.[17]

One hundred and twenty-four patients (59.9% male and 45.1% female), aged 51.6 years (range 18-80) were examined. Lymphoma (71% NHL, 29% HD) was newly diagnosed in 86.6% of the patients and the other patients (13.4%) were in relapse phase. Mean Hb was 12.9 g/dL in the NHL patients and 12.3 g/dL in the HD patients; overall 44.4% of patients had Hb ≤ 12 g/dL. FACT-An scores were significantly lower in patients with Hb ≤12 g/dL (59.7 vs 64), with a worse performance status score (59 if =0 vs 63.8 if >0), and worse stage (65.6 if stage ≤ II vs 61.2 if stage > II). FACT-An score were directly related with Hb level (Pearson r= 0.34 p=0.0001). These preliminary data are consistent with other literature reports regarding the frequency of baseline anemia in lymphoma patients. In addition, Hb level seems to be one of the crucial factors that can influence the QOL of lymphoma patients at the beginning of chemotherapy. Once the survey (baseline data along with end of chemotherapy data) is completed, it will be possible to clarify the relationship between fatigue, anemia, and outcome.

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Improving Outcomes in Elderly Non-Hodgkin's Lymphoma Patients: The Role of Epoetin α

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Among the various classes of malignant disease, lymphomas have one of the most rapidly increasing incidences. The number of diagnosed cases is growing by 5-10% annually, with a current incidence of 12-15 cases per 100,000 individuals in the US and Europe.[1,2] Since the population is aging, the incidence of non-Hodgkin's lymphoma (NHL) in elderly patients is also rising. Non-Hodgkin's lymphoma with an aggressive histology has a peak incidence in the subset of patients over 60 years old. This type of lymphoma is curable in 50% of younger patients but the cure rate is significantly lower in elderly patients.[3,4] The cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy regimen is considered the gold standard treatment for elderly patients. In the study by Dixon *et al.*,[5] the subset of elderly patients who received full-dose CHOP obtained similar responses to younger patients. The lower response rate observed in the overall population of elderly patienst must be mentioned. Only about one third of elderly patients tolerate full standard doses and the related treatment mortality is about 15-30%. The administration of sub-optimal doses of CHOP to elderly patients may contribute to reducing treatment results. The shorter survival has been ascribed to two main causes: a tendency by physicians to administer weaker, *better tolerated* (hence less effective) treatment to elderly; and poor tolerability of cytotoxic treatment, largely due to the presence of concomitant disease.[6] When making treatment decisions in older cancer patients, it is necessary to evaluate, on an individual basis, the patient's health status, tumor type, treatment goal and treatment choices. Two approaches have been proposed: the first is to give priority to the possibility of cure and use the same treatment as in the young, provided there is no severe concomitant disease contraindicating such treatment; the second is to make quality of life the priority and to use specific treatment regimens tailored to the elderly, which are reputedly less toxic but also less effective. For curable malignancies, such as aggressive NHL in the elderly, new combination therapies including cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prendisone (VNCOP-B) have been shown to prolong survival.[7] As a first therapy this regimen produced a complete response rate of 58% without significant differences among the different age subgroups (60 to 69, 70 to 79, and ≥ 80 years). However, although these treatments have an acceptable toxicity profile, elderly patients are at greater risk of neutropenic infection and anemia that are younger patients. Both these unfavorable risks can be the cause of treatment failure either because chemotherapy doses are reduced or because they are delayed. While it is well known that neutropenia is a limiting factor for chemotherapy delivery, and for this reason the addition of granulocyte colony-stimulating factor (G-CSF) in the VNCOP-B regimen is a standard practice,[8] anemia is becoming understood to be another crucial factor, often underestimated, that can influence patient's outcome and may indirectly affect survival.[9,10] Anemia has been shown to decrease quality of life in cancer patients.[11-13] It seems to have an independent impact on the biology of cancers and response to treatment, particularly radiotherapy,[14-16] and it is a negative prognostic factor in NHL.[10] Epoetin (recombinant human erythropoietin) is an established treatment for ane-

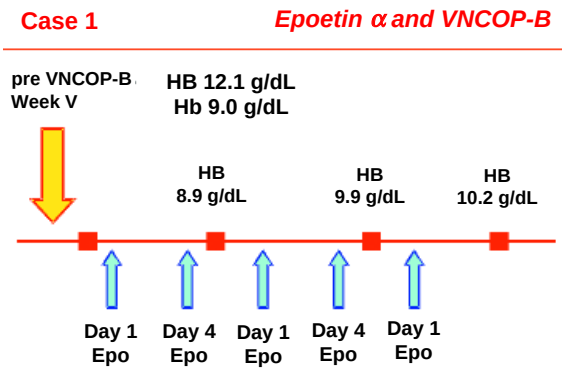

Figure 1.

mia associated with myelosuppressive chemotherapy.[17] Emerging data are addressing whether there is an association with treatment outcomes in certain settings.[15,16] We report the experience of three patients who were receiving VNCOP-B treatment and during their trial experienced a marked drop in Hb level (ranging from 7.8 g/dL to 9.5 g/dL). Due to the presence of anemia which was sufficiently severe to determine postponement or reduction of the cytotoxic therapy, chemotherapy, theoretically had to be interrupted. Our decision was to start treatment with a high dose of epoetin α (40,000 IU twice a week) and, contrary to existing practice, not interrupt chemotherapy.

This approach was supported by the fact that high doses of epoetin α rapidly corrected the Hb level (mean 1 g/dL of Hb in 2 weeks) allowing the planned dose of VNCOP-B to be delivered (Figure 1).

Based on our preliminary data, a clinical trial is being designed to evaluate the potential benefits on outcomes by correcting anemia with epoetina α in elderly NHL patients who are scheduled to receive a weekly regimen of VNCOP-B plus G-CSF.

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