Targeting Anemia in Patients with Lung Cancer

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Abstract: Anemia is highly prevalent in patients with lung cancer, often occurring at baseline and frequently exacerbated as a result of treatment with platinum-based chemotherapy. Anemia has been shown to have a negative effect on quality of life in patients with lung cancer, and additional data indicate that decreases in hemoglobin in these patients are associated with impaired survival. Multiple clinical studies have demonstrated that treatment of anemia with erythropoietic agents in patients with lung cancer results in a significant increase in hemoglobin, decrease in transfusions, and improvement in quality of life. Ongoing research is evaluating whether erythropoietic therapy can reduce cognitive impairment associated with lung cancer, cytotoxic therapy, and anemia. Despite the known adverse effects of anemia and the established benefits of erythropoietic therapy in anemic patients with lung cancer, more than half of these patients do not receive any anemia treatment. The purpose of this review is to report results of the European Cancer Anaemia Survey that describe the prevalence of anemia in patients with lung cancer, to review the major studies evaluating the clinical outcomes of erythropoietic therapy in patients with lung cancer, to discuss the recent safety concerns regarding the use of erythropoietic agents in patients with cancer treated to high hemoglobin levels, and to describe various novel therapeutic applications of erythropoietic agents in lung cancer.

Key Words: Anemia, Epoetin alfa, Erythropoietin, Lung cancer, Hemoglobin.

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Lung cancer is the most common cancer worldwide, with a prevalence nearly threefold greater in men than in women.[1] Cancer-related or cancer treatment–related anemia occurs frequently in patients with lung cancer,[2,3] with one comprehensive review reporting incidences of anemia (hemoglobin [Hb] ≤12 g/dL) and severe anemia (Hb <8 g/dL) as high as 100% and 55%, respectively, in patients with lung cancer receiving chemotherapy.[2] One major factor contributing to anemia in patients with lung cancer is the use of platinum-based chemotherapy, a regimen that results in clinically meaningful decreases in Hb,[2] as first-line chemotherapy for lung cancer.[2,4,5] The severity of anemia in these patients is dependent on disease stage, as well as the duration, type, and intensity of chemotherapy.[6] The National Cancer Institute (NCI) and the World Health Organization (WHO) have established criteria for the classification of the severity of anemia related to cancer therapy (Table 1).[2] These criteria each grade the severity of anemia on a 0 (within normal limits) to 4 (life-threatening) scale.

Anemia in patients with cancer contributes to fatigue and other symptoms that can impair health-related quality of life (QOL).[7–9] The adverse consequences of anemia may be particularly important in lung cancer because these patients have been shown to have higher incidences of anemia and transfusion for anemia than patients with other solid tumors[2,10,11] and often have comorbid conditions, such as cardiovascular and pulmonary disease,[12] that may worsen anemia symptoms and impair tolerance of Hb decreases. In open-label, community-based studies as well as a randomized, double-blind, placebo-controlled trial, treatment of anemia with recombinant human erythropoietin (epoetin alfa) in patients with cancer receiving chemotherapy with or without radiation therapy produced significant increases in Hb, significant decreases in transfusion requirements, and significant and clinically meaningful improvements in QOL.[13–19] Increases in Hb in these studies were associated with improvements in QOL,[15–20] and further studies showed the greatest incremental improvement in QOL occurred when Hb increased from 11 to 12 g/dL during epoetin alfa therapy.[21,22] Other investigators have suggested that anemia is an independent prognostic factor for survival in patients with lung cancer.[23–26] Therefore, strategies to correct anemia in these patients may be beneficial in improving therapeutic outcomes in addition to improving QOL.

The purpose of this review is to report the prevalence of anemia in patients with lung cancer, to review the major studies evaluating the clinical outcomes of erythropoietic therapy in patients with lung cancer, to discuss the recent safety concerns of erythropoietic agents in patients with cancer treated to high Hb levels, and to describe the potential role of erythropoietic therapy in attenuating cognitive impairment in patients with lung cancer.

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TABLE 1. National Cancer Institute (NCI) and the World Health Organization (WHO) Toxicity Criteria for Anemia[2]

Severity	NCI (Hb, g/dL)	WHO (Hb, g/dL)
Grade 0	WNL	>11.0
Grade 1 (mild)	10.0 to WNL	9.5–10.9
Grade 2 (moderate)	8.0–10.0	8.0–9.4
Grade 3 (serious/severe)	6.5–7.9	6.5–7.9
Grade 4 (life threatening)	<6.5	<6.5

Hb, hemoglobin; NCI, National Cancer Institute; WHO, World Health Organization; WNL, within normal limits.

Adapted with permission from Pohl GMI, Ludwig H. Supportive treatment for anemic cancer patients. *Wien Med Wochenschr* 2004;154:226–234.

PREVALENCE OF ANEMIA IN LUNG CANCER: THE EUROPEAN CANCER ANAEMIA SURVEY (ECAS)

The ECAS was a prospective, observational, epidemiologic survey that assessed the prevalence, incidence, and treatment of anemia (Hb <12 g/dL); risk factors for developing anemia; and the relationship between anemia and WHO performance status in European patients with cancer.[3] The survey was conducted during 2001 in about 750 centers in 24 countries; patients were followed for as long as 6 months. Of 15,367 enrolled patients, 2176 had lung cancer and provided data for baseline characteristics (i.e., the enrollment population) (median age, 62 years; 76% male; 70% with WHO performance status 0 or 1).[27] Of the 2176 patients, 119 were excluded from further analysis because of inconsistent diagnosis and treatment; thus, 2057 patients with lung cancer were included in the assessable population. Of the assessable population, 1900 patients had at least one evaluation following enrollment and were included in the analysis population.[27]

Of the enrollment population ($n = 2176$), 63% of patients overall had newly diagnosed lung cancer and 53% had never received treatment for lung cancer.[27] In the assessable population ($n = 2057$), 2002 patients had assessable baseline Hb data; 38% (753/2002) of these patients were anemic at enrollment. Baseline anemia was present in 31% of untreated patients, 32% of patients receiving radiation therapy, 39% of patients receiving chemotherapy, and 50% of patients receiving concomitant chemotherapy/radiation therapy. In patients with anemia at enrollment, lower baseline Hb was significantly correlated (Spearman's $r = -0.124$; $p < 0.001$) with poorer baseline WHO performance status.[27]

Of the 1900 patients included in the analysis population, 1462 (77%) developed anemia at some point during the survey.[27] Anemia was most prevalent among patients receiving chemotherapy (956/1147; 83%) or nonconcomitant combination chemotherapy/radiation therapy (342/407; 84%) (Figure 1). Of the 1462 patients who developed anemia during the survey, Hb nadirs were less than 9.0 g/dL in 21% of patients and 9.9 g/dL or less in 46% of patients. Of the 1147 patients who underwent chemotherapy during the survey, anemia occurred slightly more frequently among patients receiving platinum chemotherapy (692/818; 85%) compared with nonplatinum chemotherapy (264/329; 80%). With respect to anemia treatment, 53% (507/956) of anemic patients undergoing chemotherapy received no anemia treatment, 24% received erythropoietic therapy (mean Hb at initiation, 9.1 g/dL), 18% received red blood cell transfusion (mean Hb at initiation, 8.5 g/dL), and 5% received iron only. Logistic analysis revealed that the risk of developing anemia in these lung cancer patients was doubled by treatment with platinum-based chemotherapy (adjusted odds ratio = 2.1; $p = 0.0002$) or by being female (adjusted odds ratio = 1.7; $p = 0.0129$).[27]

Of the patients who were not anemic or receiving anemia treatment at enrollment and who initiated cancer treatment and underwent at least two cycles of therapy during the survey (total $n = 485$ [chemotherapy, $n = 417$; radiation therapy, $n = 55$]), 71% became anemic during the survey.[27] The incidence of anemia in these patients was 80% for those receiving chemotherapy, 31% for those receiving concomitant chemotherapy/radiation therapy, and 15% for those re-

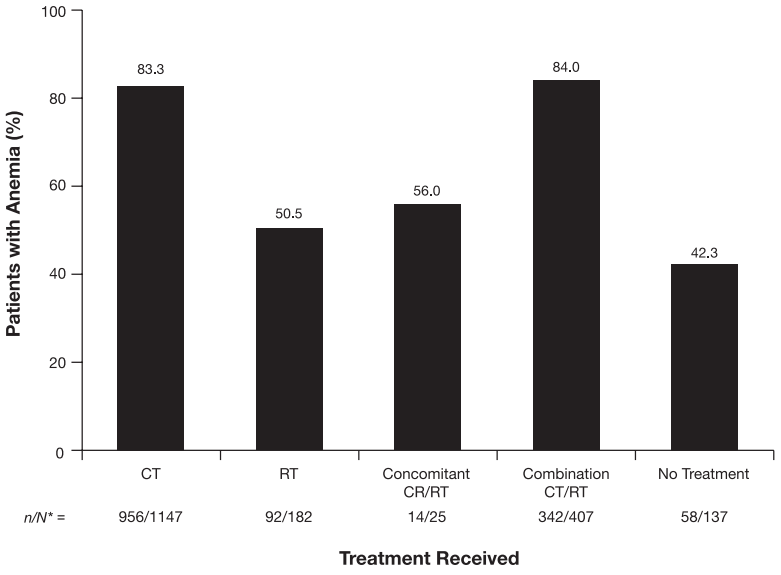

FIGURE 1. Frequency of anemia by cancer treatment during the European Cancer Anaemia Survey.[27] CT, chemotherapy; RT, radiation therapy. *Analysis population, $n = 1900$ (missing data for two patients). Combination CT/RT refers to administration of CT and RT at different times (i.e., not concomitantly).

