Is Darbepoietin Alfa Linked to Mortality During Non-Small Cell Lung Cancer Chemotherapy?

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Patients with metastatic NSCLC frequently suffer from anemia,1 defined by a hemoglobin level (Hb) of 12 g/dL or less or a rapid decrease of Hb by at least 2 g/dL. For these patients, anemia may occur through different mechanisms: chemotherapy-induced anemia is the topic of this brief editorial and is a major etiology.2 However, alternative causes are frequently observed: anemia related to other therapies (e.g., radiotherapy) and anemia directly induced by host-tumor interactions3 such as inflammatory processes and their consequences, functional or absolute iron deficiency, malnutrition and vitamin deficiency, and chronic tumor hemorrhage. Dealing with anemia is an important concern for treatment of NSCLC, as many patients with NSCLC are anemic at the time of diagnosis and thus have a higher risk of developing severe anemia during the course of chemotherapy.4 Moreover, first-line chemotherapy of NSCLC is platinum-based and this class of drugs is a strong anemia inducer through both myelosuppression and reduced kidney erythropoietin release.5 In addition, anemia is frequently symptomatic in patients with NSCLC as a consequence of their cardiac and respiratory comorbidities, which increase dyspnea, tachycardia, and fatigue.1

Packed red blood cells (PRBC) transfusion has been the first therapy introduced to correct anemia in cancer; it remains the quickest way of correcting anemia and might be considered in patients with a Hb of less than 8 g/dL or in cases of symptomatic severe anemia.2,5 However, the risks associated with PRBC transfusions, such as iron overload, circulatory overload, viral or bacterial transmission, or human leukocyte antigen immunization, limit its use. Erythropoiesis-stimulating agents (ESAs) have been developed to reverse chemotherapy-induced anemia and its consequences such as reduced quality of life (QOL), fatigue, shortening of chemotherapy programs, and compromised efficiency of treatment.1,6,7 Beyond the efficacy of ESA therapy in reaching their primary objective, that is, reducing the number or patients who require PRBC transfusion and sustaining Hb above 10 g/dL, there was a hope that they could also improve survival outcome of patients. Several reasons explained this optimism: although patients with anemia have an increased risk of death, PRBC transfusion seems to overcome the negative prognostic effects of displaying low Hb count and seems to restore a similar survival to that of nonanemic patients.5,20 Hence, the hypothesis was that ESAs could act in the same way; obviously, increasing the safety of chemotherapy might also increase its chance of efficacy. Finally, some early preclinical studies have suggested that ESAs improve the efficiency of chemotherapy by limiting tumor hypoxemia, a critical mechanism of tumor chemo-resistance. Tumor oxygenation may be improved through the administration of recombinant erythropoietin, an improvement that seemed to be independent of its effects on Hb.9 Unfortunately, several randomized studies of ESAs versus placebo or no treatment in patients receiving chemotherapy for different solid tumors such as head and neck tumors10 and gynecologic cancers,11,12 together with meta-analyses,13,14 have sent a warning message to oncologists: an increased mortality risk was suggested in patients receiving ESAs when compared with placebo. Among the different but not mutually exclusive hypotheses for such a paradoxical observation are the increased risk of thrombotic venous events (TVE), the generation of neutralizing antibodies with its rare consequence, pure red cell aplasia, and the theoretical risk of erythropoietin-induced tumor growth. The latter risk has been a subject of controversy. On one hand,
there are erythropoietin receptors on some tumor cells, but on the other hand, these receptors seem to be nonfunctional.\textsuperscript{15} In summary, preclinical data do not support a strong direct or indirect effect of ESAs on tumor growth.\textsuperscript{15} Besides, an updated and recent meta-analysis did not identify a detrimental survival effect of ESAs and suggested that previous observations were the results of a misuse of ESAs in nonanemic patients or in patients not receiving myelosuppressive therapy.\textsuperscript{16} Considering the conflicting data regarding the ESA therapy (i.e., survival relationship), several programs have been implemented, namely risk evaluation and mitigation strategies, a program built by Food and Drug Administration (FDA) to determine whether the benefits from ESA outweighed the risk of increased mortality. In 2017, the FDA declared that the risk evaluation and mitigation strategies program was no longer necessary. FDA also required a formal evaluation of the putative increased mortality risk in patients receiving epoietin alfa (EPO) and darbepoietin alfa (DPO), two different ESAs, in placebo- or no treatment-controlled phase 3 studies. A former study conducted in breast cancer comparing EPO and its placebo, with progression-free survival (PFS) as a primary end point, failed to demonstrate noninferiority of EPO over placebo.\textsuperscript{17} However, the late separation of PFS curves noted in this study is not completely explained by the ESA that was delivered at the beginning of therapy.

In this issue of the \textit{Journal of Thoracic Oncology}, Gascón et al.\textsuperscript{18} reported a randomized double-blind study comparing DPO to its placebo in patients with NSCLC receiving first-line chemotherapy.\textsuperscript{18} This study followed a noninferiority design taking into account overall survival as primary end point with a 1.15 threshold for the upper confidence interval. A total of 2516 patients were randomized, with a 2:1 ratio, at the time of randomization. The investigators explained that the protocol indicates that patients were receiving a first-line myelosuppressive cyclic chemotherapy and had not received prior adjuvant or neoadjuvant therapy for NSCLC, it is pointed out in the result section that most of them (68%) had undergone previous chemotherapy. This is not contradictory as this subgroup of “previously treated” patients are those enrolled while the first-line chemotherapy was ongoing, reflecting the “real-world” practice. One can hypothesize that the local Hb level for many patients reflected nadir Hb value of an ongoing cycle of chemotherapy and that the centrally tested value, taken at the time of randomization, reflected the spontaneous recovery. In these circumstances, IVRS instructed to temporarily withhold investigational product until Hb fell to 12.0 g/dL and below, the investigators explained in the point-by-point letter. Is this important? As long as there is no imbalance of this criterion between DPO and placebo groups, and as long as this is a placebo-controlled study, the bias is negligible. Despite withholding treatment in some patients, the median treatment period as measured from day 1 was about 3 months (91 d for placebo, 92 d for darbepoietin alfa, 92 d overall). This treatment period is long enough to fairly evaluate survival effect of darbepoietin.

As consequences of anemia are worse in patients with lung cancer than in those with other solid tumors,
owing to frequent concomitant chronic obstructive pulmonary disease and/or coronary insufficiency, interventions reversing fatigue and other anemia-related symptoms should have a positive effect on QOL as assessed by dedicated scales such as the Functional Assessment of Cancer Therapy-Anemia. This study would have been an opportunity to measure the QOL improvement but unfortunately did not. One can hypothesize that a quality-adjusted life-year of the survival (i.e., considering the QOL in weighting the survival difference between DPO and placebo) might allow the demonstration of a survival benefit with DPO. Nevertheless, other studies conducted in lung cancer and other malignancies have shown the positive effect of correction of Hb level on QOL. The scores on the Functional Assessment of Cancer Therapy-Anemia subscale also clearly differentiate patients with low or high Hb levels.

A final point of interest is the population of the study itself. Patients included in this study were undergoing their first line of chemotherapy. In total, 95% of them have received a platinum-based chemotherapy, mostly carboplatin-based, reflecting good agreement of this population with clinical guidelines and also high exposure to cancer-induced anemia. Few noneligibility criteria were mentioned in the study design. With a DPO group median overall and PFS of 9.46 and 4.44 months respectively, the survival curves reflected the outcome of an unselected population of NSCLC, an outcome poorer than those observed in recent phase III studies testing new strategies in selected patients. Therefore, the study by Gascón et al. is a relevant ensign into the risk-to-benefit ratio of DPO in the daily practice for patients not eligible for first-line immunotherapy or targeted therapy.

With the introduction of combined immunochemotherapy in the techniques of NSCLC therapy, complex mechanisms of anemia emerge, such as immune checkpoint inhibitor-induced hemolytic anemia or even pure red cell aplasia. As standard first-line systemic therapy for NSCLC quickly evolves, further studies are warranted to define the risk-to-benefit ratio of ESA for patients receiving these new treatment modalities.

References

