Clinical significance of anemia as a prognostic factor in non-small cell lung cancer carcinoma with activating epidermal growth factor receptor mutations

Hye Seon Kang[1], Ah Young Shin[2], Chang Dong Yeo[3], Chan Kwon Park[4], Ju Sang Kim[2], Jin Woo Kim[5], Seung Joon Kim[6,7], Sang Haak Lee[3,7], Sung Kyoung Kim[8]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [6]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [7]Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [8]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Contributions: (I) Conception and design: HS Kang, CD Yeo, SK Kim; (II) Administrative support: AY Shin, JS Kim; (III) Provision of study materials or patients: CK Park, JW Kim, SJ Kim; (IV) Collection and assembly of data: HS Kang, AY Shin, SK Kim; (V) Data analysis and interpretation: HS Kang, CD Yeo, SH Lee, SK Kim; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sung Kyoung Kim, MD, PhD. Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon, Gyeonggi-do, 16247, Republic of Korea. Email: kimskmd@gmail.com.

Background: Anemia is a frequent finding in cancer patients. Pre-treatment anemia is known to be associated with poor survival after surgery or stereotactic body radiation therapy of non-small cell lung cancer (NSCLC). However, little study was conducted in NSCLC with activating epidermal growth factor receptor (EGFR) mutations.

Methods: This was a multicenter retrospective study conducted in seven university teaching hospitals in the Republic of Korea from January 2009 to February 2016. A total of 290 patients were diagnosed with NSCLC harboring sensitizing EGFR mutations and treated with EGFR-tyrosine kinase inhibitor (TKI) as 1st line. Of these patients, 104 met the exclusion criteria. Pre-treatment anemia was defined according to World Health Organization criteria (Hb concentration <13 g/dL for men and <12 g/dL for women).

Results: A total of 186 patients were finally included for analysis. Of these patients, 86 (46.2%) and 100 (53.8%) patients were classified into anemia and non-anemia groups, respectively. The anemia group had shorter median overall survival (OS) than the non-anemia group [24.83 (95% CI, 17.49–32.17) months *vs.* 42.10 (95% CI, 31.87–52.34) months, P=0.031]. In multivariate analysis, anemia (aHR, 2.573; 95% CI, 1.122–5.901; P=0.026) was only independent factors for poor OS.

Conclusions: Our study suggests that pre-treatment anemia is a significant poor prognostic factor for OS of NSCLC patients with EGFR mutations treated with EGFR-TKI.

Keywords: Anemia; non-small cell lung carcinoma (NSCLC); EGFR tyrosine kinase inhibitor (TKI)

Introduction

Anemia is a frequent finding in cancer patients. About 38% of lung cancer patients have anemia. Cancer-related anemia results from various conditions such as malnutrition, disease progression, renal or bone marrow involvement, coexisting inflammation, and oncologic treatment including chemotherapy and radiotherapy (1,2). Cancer cells can produce inflammatory cytokine such as interleukin-6 (IL-6) that can directly and indirectly lead to anemia by inhibiting erythropoiesis (3). Proinflammatory cytokine, mainly IL-6 promote alterations in erythroid progenitor proliferation, erythropoietin production and survival of circulating erythrocytes. Cancer related anemia is commonly occurred in patients at advanced disease and advancing age. Prevalence of anemia differs among cancer types, and lung cancer, gynecologic or gastrointestinal tumors are highly accompanied (4).

Pre-treatment anemia is a poor prognosis factor in various malignancies including soft tissue sarcoma, glottis larynx, pancreas, colon, breast and ovarian cancer (5-8). In lung cancer, anemia and transfusion for anemia correction are associated with poor survival after surgery of non-small cell lung cancer (NSCLC) (9). In patients with early-stage lung cancer who have undergone stereotactic body radiation therapy (SBRT), pre-treatment anemia is predictive of poor overall survival (OS) and disease progression (10). In lung cancer including NSCLC and small cell lung carcinoma, pre-treatment anemia is associated with shorter median survival time (11).

In the era of molecular targeted therapy, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) has shown remarkable outcomes with minimal side effects compared to conventional chemotherapy (12). In locally advanced NSCLC, especially patients with old age or poor performance status (PS), EGFR-TKI has shown similar efficacy comparable to chemotherapy, the standard treatment (13).

Multiple prognostic factors including sex, histology, clinical stage, the presence of pleural effusion or brain metastasis, PS, body mass index (BMI) and prognostic nutritional index have been evaluated in NSCLC patients with activating EGFR mutations (14). Although pre-treatment anemia is a known prognostic marker for survival and clinical outcomes of patients treated with cytotoxic chemotherapy, surgery, or SBRT, few studies have been conducted in NSCLC patients treated with EGFR-TKI. Thus, the objective of this study was to investigate the prognostic value of pre-treatment anemia in NSCLC patients with activating EGFR mutations treated with EGFR-TKI.

Methods

This was a multicenter retrospective study conducted in seven hospitals of the Catholic Medical Center in South Korea: Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital, Eunpyeong St. Mary's Hospital, Bucheon St. Mary's Hospital, Uijeongbu St. Mary's Hospital, St. Vincent's Hospital, and Incheon St. Mary's Hospital. All data were collected from hospital database.

Patients

Patients were eligible if they were diagnosed from January 2009 to February 2016 with histologically confirmed, primary NSCLC [International Classification of Diseases for Oncology (ICD): C34.X] and EGFR mutation positive advanced NSCLC treated at our institutions. Use of TKI was investigated using drug codes for iressa, gefitinib, or afatinib during study period. Patients who were transferred to other centers or treated with EGFR-TKI as 2nd line were excluded. The study flow is summarized in *Figure 1*. The follow-up period ended on December 31, 2017.

Data

We extracted the following data from patient medical records: patient demographics, smoking history, stage of lung cancer, comorbid diseases, Eastern Cooperative Oncology Group (ECOG) PS, laboratory data, history of chemotherapy and/or radiation, survival status, and dates of disease progression and death. Blood samples drawn to evaluate hemoglobin level within one month before EGFR-TKI treatment were used to compile a pretreatment hematologic profile for each patient using laboratory value most proximal to EGFR-TKI treatment. Pre-treatment anemia was defined according to World Health Organization (WHO) criteria (Hb concentration <13 g/dL for men and <12 g/dL for women) and tested before EGFR TKI treatment in a month (15). Anemia was divided into mild and moderate anemia according to the scoring system provided by the National Cancer Institute and the National Institutes of Health: mild anemia, hemoglobin level of 10.0–11.9 g/dL for women and 10.0–12.9 g/dL for men; moderate anemia, hemoglobin
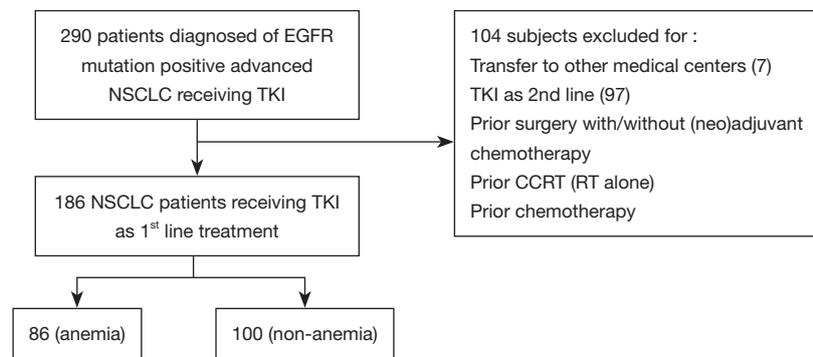
Figure 1 Study flowchart. NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; CCRT, concurrent chemoradiation therapy.

level of 8.0–9.9 g/dL (16). Simplified Comorbidity Score (SCS) comorbidity items were defined according to Colinet *et al.* (17). Items of SCS and their weighing based on risk of death resulted in seven comorbidity groupings as follows: tobacco consumption (weighing: 7), diabetes mellitus (weighing: 5), renal insufficiency (weighing: 4), respiratory comorbidity (weighing: 1), cardiovascular comorbidity (weighing: 1), neoplastic comorbidity (weighing: 1), and alcoholism (weighing: 1).

Statistical analysis

Baseline demographics and clinical outcomes were compared between patients with anemia and non-anemia. We used Pearson's chi-square test to compare discrete variables and Student's t-test or analysis of variance to compare continuous variables. The Mann-Whitney test was used to compare median value. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated for predictors that were significant in multivariate Cox regression analysis. A two-sided P value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows software (ver. 20.0; IBM Corp., Armonk, NY, USA).

Results

Overall, 290 patients were diagnosed with NSCLC harboring activating EGFR mutations and treated with EGFR-TKI, of whom 104 met the exclusion criteria (transferred to another medical center or treated with EGFR-TKI as 2nd line treatment). Thus, 186 patients were finally included in our analysis (*Figure 1*). The mean age of included subjects was 67.51±11.65 years (range,

39–97 years). There were 64 (34.4%) males. Of all included patients, 86 (46.2%) and 100 (53.8%) were classified into anemia and non-anemia groups, respectively. In anemia patients, 15 (8.1%) had moderate and 69 (38.2%) had mild severity of anemia based on the scoring system of the National Cancer Institute and the National Institutes of Health. In patients with anemia, we compared these two groups and explored clinical factors predicting OS. Total and median follow-up time were 19.4 and 15.2 person-months, respectively.

Baseline characteristics of these two groups are summarized in *Table 1*. The proportion of male was lower in the anemia group (26.7% *vs.* 41.0%, P=0.045). The rate of poor PS (≥2) based on ECOG PS was higher in the anemia group (29.5% *vs.* 11.4%, P=0.010). Mean age was higher in the anemia group (70.62±11.58 *vs.* 64.86±11.10 years, P<0.001). Smoking history, cancer staging, and sensitizing EGFR expressions showed no significant differences between the two groups.

Patients with anemia group displayed a shorter median OS than those with non-anemia [24.83 (95% CI, 17.49–32.17) months *vs.* 42.10 (95% CI, 31.87–52.34) months, P=0.031)]. However, there was no difference in progression free survival (PFS) between anemia and non-anemia group [10.27 (95% CI, 7.98–12.55) months *vs.* 10.93 (95% CI, 9.14–12.73 months, P=0.865). When the patients with anemia group were divided into two subgroups, mild and moderate anemia based on the severity of anemia, moderate anemia group had the shortest OS among the three groups (10.03±3.82 *vs.* 27.23±3.56 *vs.* 42.10±4.89 months, P=0.001) (*Figure 2*).

In univariate analysis for OS, HR was 1.934 (95% CI, 1.220–3.07, P=0.005) for male, 1.029 (95% CI, 1.006–1.052, P=0.012) for older age, 1.657 (95% CI, 1.049–

Table 1 Comparison of patient characteristics according to anemia

Characteristic	Non-anemia (n=100)	Anemia (n=86)	P value
Gender, male	41 (41.0)	23 (26.7)	0.045
Age (years)	64.86±11.10	70.62±11.58	0.001
[a]Hemoglobin	13.55 (12.0–17.4)	11.05 (8.1–12.6)	<0.001
Smoking status			0.196
Never-smoker	66 (66.7)	65 (75.6)	
Current/former smoker	33 (33.7)	21 (24.4)	
Initial stage			0.846
III	18 (18.0)	14 (16.3)	
IV	82 (82.0)	72 (83.7)	
Brain metastasis	34 (34.3)	32 (37.2)	0.759
EGFR mutations			0.688
Ex19del	52 (52.0)	45 (52.3)	
L858R	39 (39.0)	35 (40.7)	
[b]Minor	9 (9.0)	6 (7.0)	
EGFR-TKI			0.456
Gefitinib	76 (76.8)	69 (82.1)	
Erlotinib	20 (20.2)	11 (13.1)	
Afatinib	4 (4.0)	5 (5.8)	
ECOG PS ≥ 2	9 (11.4)	23 (29.5)	0.010

Values are presented as number (%) or mean ± standard deviation. [a], values are presented as median value (Min-Max); [b], including G719A, G719S, G719X, L861Q, L861X, and exon-20 insertions. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
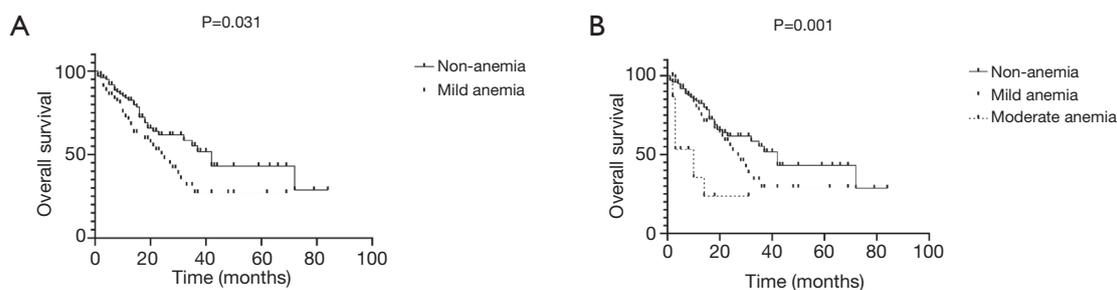

Figure 2 Kaplan-Meier curves for overall survival according to presence of anemia at diagnosis (A) and the severity of anemia (B) in non-small cell lung cancer patients with epidermal growth factor receptor mutation.

2.617, P=0.031) for anemia, 1.061 (95% CI, 1.022-1.102, P=0.002) for higher NLR, 1.034 (95% CI, 1.019–1.049) for higher PLR, 1.812 (95% CI, 1.037–3.165, P=0.037) for smoking status, 3.329 (95% CI, 1.443–7.682, P=0.005) for stage IV compared to stage III, 2.043(95% CI, 1.294–3.226, P=0.002) for SCS equal to or higher than 5, and 2.506 (95% CI, 1.449–4.334, P=0.001) for poor PS. In multivariate analysis, anemia (aHR, 2.573; 95% CI, 1.122–5.901; P=0.026) was only independent factors for poor OS (*Table 2*).

Table 2 Univariate and multivariate analysis of the clinicopathologic variables affecting mortality in patients with EGFR mutations receiving EGFR-TKIs

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male *vs.* female	1.934	1.220–3.07	0.005	2.177	0.794–5.972	0.131
Age (years)	1.029	1.006–1.052	0.012	1.012	0.980–1.046	0.460
Anemia *vs.* non-anemia	1.657	1.049–2.617	0.031	2.573	1.122–5.901	0.026
NLR	1.061	1.022–1.102	0.002	0.941	0.754–1.090	0.594
PLR	1.034	1.019–1.049	<0.001	1.037	0.986–1.090	0.156
Smoking current + former *vs.* none	1.812	1.037–3.165	0.037	1.613	0.377–6.895	0.519
Initial stage (IV *vs.* III)	3.329	1.443–7.682	0.005	3.635	0.808–16.356	0.093
EGFR mutations Non-sensitizing *vs.* sensitizing	1.316	0.674–2.570	0.422	1.551	0.494–4.872	0.453
Brain metastasis	1.237	0.775–1.974	0.372	1.308	0.608–2.811	0.492
SCS ≥5 *vs.* <5	2.043	1.294–3.226	0.002	2.186	0.744–6.419	0.155
ECOG PS ≥2 *vs.* <2	2.506	1.449–4.334	0.001	1.250	0.446–3.504	0.672

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SCS, simplified comorbidity score; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Discussion

We compared clinical outcomes of patients with NSCLC harboring activating EGFR mutations treated with EGFR-TKI based on hemoglobin levels and explored prognostic clinical factors for treatment outcomes. In the present study, we found that 46.2% of 186 cancer patients had anemia at the time of diagnosis. We also found that the proportion of male was lower in the anemia group while poor PS and mean age were higher in the anemia group. Patients with anemia displayed shorter median OS than those with non-anemia. When patients with anemia were divided into mild and moderate anemia subgroups based on the severity of anemia, the moderate anemia group had the shortest OS among the three groups. In multivariate analysis, anemia was only independent factor for poor OS.

Anemia is a common hematological manifestation of cancer (1,2,18). Anemia is considered a side effect associated with chemotherapy. However, many cancer patients already have anemia before the start of any treatment (18). Pre-treatment anemia can negatively influence clinical outcomes in various types of malignancies including soft tissue sarcoma, pancreatic cancer and ovarian carcinoma (19,20). Low hemoglobin contributes to inadequate oxygenation of squamous cell carcinoma of the head and neck and increased

resistance to radiotherapy (21). In lung cancer, anemia at diagnosis of the disease is associated with reduced median survival time (11). Pre-treatment anemia is associated with poor survival and non-local disease progression in patients with SBRT (10). Peri-operative anemia and blood transfusion for anemia correction are also associated with shorter recurrence free survival and OS after NSCLC surgery (9).

Known clinical factors affecting prognosis are sex, histology, clinical stage, the presence of pleural effusion, and PS in NSCLC with EGFR mutations receiving EGFR-TKI as 1st line treatment (22). In NSCLC patients with EGFR mutations receiving EGFR-TKI regardless of the order of treatment, ECOG PS, brain metastasis, low BMI, and prognostic nutritional index are poor prognostic factors for OS (14). In EGFR-mutant NSCLC patients who are re-administered TKIs after failure of first-line TKIs, systemic inflammatory status in terms of neutrophil-to-lymphocyte ratio and lymphocyte-to-monocyte ratio are prognostic factors (23). However, little data exist about the prognostic role of anemia in NSCLC patients with EGFR mutations treated with EGFR-TKI.

There are many causes for anemia. It involves nutritional status and other comorbidities. A direct link between anemia and poor prognosis in NSCLC patients is difficult

to explain. One possible mechanism is inflammatory cytokine IL-6. IL-6 is a cytokine that plays an important role in many chronic inflammatory diseases. Most NSCLC cell lines produce IL-6 (3). IL-6 expression is involved in the regulation of tumor growth and metastasis. Activation of the IL-6R/JAK1/STAT3 pathway is known to induce resistance to irreversible EGFR-TKI in NSCLC harboring T790M (24). IL-6 is also a potent inducer for the production of hepcidin, a key regulator of iron metabolism (25). Elevation of hepcidin can lead to reduction in iron levels and results in anemia (26). Higher hepcidin levels are also associated with more aggressive disease (27).

Angiogenesis is a major prognostic factor in cancer. It is regulated by vascular endothelial growth factor (VEGF). Clinically, cancer patients with elevated levels of VEGF have worse prognosis compared to patients with normal VEGF levels (28). Tumor hypoxia and serum concentration of VEGF are strongly correlated with each other, presenting a main stimulus for angiogenesis in tumors (29). Also, anemia and poor tissue oxygenation are associated in head and neck cancers (21). In patients with untreated solid cancers of various malignancies including head and neck, cervix, rectum, and lung cancers, anemic patients have elevated levels of VEGF (30).

EGFR and VEGF signaling pathways are closely connected to each other. The expression of VEGF is up-regulated by EGFR phosphorylation (31). EGFR-TKI resistance is associated with increased expression of VEGF. A combination of VEGF inhibitor bevacizumab with EGFR-TKI can abrogate primary resistance and demonstrate substantial antitumor activity (32). Although our study did not investigate the association between anemia and VEGF expression, it might be one of mechanisms that can explain the poor prognosis in the anemia group.

Limitations

This study has some limitations. First, it was a retrospective study. Nonetheless, our study was a multi-center study having a moderate sample size. Second, the proportion of poor PS was higher in the anemia group. Cancer-related anemia results from multiple causes such as malnutrition, deteriorated intestinal absorption and metabolism, chronic inflammation, aging, and advanced stage, which are factors for decreased erythropoiesis (33). In addition to anemia, aging and malnutrition might contribute to poor prognosis. However, after adjusting for age and poor PS, anemia was an independent prognostic factor in NSCLC with EGFR

mutations treated with TKI.

Conclusions

Findings of this study showed that pre-treatment anemia is significantly associated with decreased OS in NSCLC patients with EGFR mutations treated with EGFR-TKI. Our data indicate that hemoglobin level routinely measured during cancer work up may represent a potentially important variable to predict prognosis in NSCLC patients harboring activating EGFR mutations treated with EGFR-TKI. Further large-scale prospective studies are required to validate our findings.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by institutional review boards (IRBs) of all participating centers. The requirement for informed consent was waived by IRBs because the study was based on retrospective chart reviews (IRB No HC19RCDI0027).

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