ANTICANCER RESEARCH *35*: xxx-xxx (2015)

No: 18398-G
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☐ Experimental
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☐ Epidemiological

Levels of Vascular Endothelial Growth Factor in Serum and Pleural Fluid Are Independent Predictors of Survival in Advanced Non-small Cell Lung Cancer: Results of a Prospective Study

IOANNIS GKIOZOS, SOFIA TSAGOULI, ANDRIANI CHARPIDOU, DIMITRA GRAPSA, ELIAS KAINIS, CHRISTINA GRATZIOU and KONSTANTINOS SYRIGOS

Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, Greece

Abstract. *Aim: To further evaluate the prognostic significance of pretreatment serum and pleural fluid levels of vascular endothelial growth factor VEGF in patients with non-small cell lung cancer (NSCLC) presenting with malignant pleural effusion (MPE). Patients and Methods: Forty consecutive newly diagnosed patients with NSCLC with MPE at presentation but without distant metastases were prospectively enrolled. The prognostic value of serum and pleural fluid VEGF levels for overall survival (OS) and progression-free survival (PFS) was assessed by Cox regression analysis. Results: The median serum VEGF level was significantly higher in patients as compared to healthy controls ($p<0.001$). Serum VEGF higher than 375 pg/ml, pleural fluid VEGF greater than the median value and the presence of progressive disease were all significantly associated with reduced OS and PFS, both in univariate and multivariate analyses. Conclusion: The results of our study suggest that increased pretreatment serum and pleural fluid levels of VEGF may be independent predictors of a worse survival in patients with advanced-stage NSCLC.*

Non-small cell lung cancer (NSCLC) is an aggressive malignancy, typically characterized by rapid growth, tendency for early metastatic spread and resistance to conventional chemotherapy. The majority of cases present with locally advanced or distant metastatic disease at the time of diagnosis, precluding curative surgical resection of the primary tumor (1). Despite recent advances in treatment of advanced NSCLC, including the advent of patient-tailored targeted therapies, the overall prognosis of these patients remains poor, with a median survival of less than 12 months in most series (2).

Angiogenesis is defined as the growth of new blood vessels stemming from pre-existing vasculature, and is a dynamic process controlled by a fine balance between proangiogenic and antiangiogenic factors (2). As shown by experimental and clinical data, angiogenesis plays a critical role not only in physiological events (such as embryonal development and wound healing), but also in the development, growth and metastasis of a variety of solid tumors, including NSCLC (3-5). Vascular endothelial growth factor (VEGF) is among the key proangiogenic signaling proteins involved in regulation of endothelial cell proliferation and migration, vascular permeability and stromal degradation, thereby enhancing the formation of new blood vessels, penetration of tumor cells through vessel walls and their metastatic dissemination (6-10). In recent years, immunohistochemical evaluation of VEGF expression in tumor tissue (11-13), as well as quantitative measurement of VEGF levels in the plasma, serum or other body fluids of patients with NSCLC (3, 6, 14-18), have attracted considerable research interest as potential indicators of treatment response and overall prognosis. Likewise, from a therapeutic standpoint, VEGF-targeted agents, such as the monoclonal antibody to VEGF bevacizumab, are increasingly used in combination with chemotherapy for treatment of advanced NSCLC (19, 20).

Most, but not all, previous studies have suggested that higher pretreatment serum VEGF levels may be associated with reduced survival in patients with NSCLC (2, 3, 14, 16, 21), in accordance with the results of similar studies on other solid tumor types (22-24). However, the independent

Correspondence to: Konstantinos Syrigos, MD, Ph.D., Professor and Head, Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Mesogion 152, 115 27 Athens, Greece. Tel: +30 2107475034, Fax: +30 2107781035, e-mail: ksyrigos@med.uoa.gr

Key Words: Angiogenesis, non-small cell lung cancer, pleural fluid, serum, VEGF.