Sorafenib in Patients with Advanced Non-small Cell Lung Cancer that Harbor K-Ras Mutations

A Brief Report

Egbert F. Smit, Anne-Marie C. Dingemans,† Frederik B. Thunnissen,‡ Monique M. Hochstenbach,† Robert-Jan van Suylen,§ and Pieter E. Postmus**

The current standard of therapy for patients with advanced non-small cell lung cancer (NSCLC) is platinum-based doublet chemotherapy. Therapeutic results are far from satisfactory: survival has reached a plateau at a median of 9 to 11 months in the recently published phase III trials. One way to improve on these results is to personalize treatment, among others based on tumor or molecular characteristics. Examples of these are the use of pemetrexed for nonsquamous NSCLC[1] and tyrosine kinase inhibitors for tumors harboring epidermal growth factor receptor (EGFR) mutations.[2] In NSCLC, the most frequently occurring somatic mutations are located in three codons of the *K-Ras* gene.[3] Constitutional activation of K-Ras leads to signaling through the Raf-Mek-Erk pathway, which is implicated in cellular growth and survival pathways. Treatment options for patients who have K-Ras mutated tumors are limited as these are believed to be poor responders to cytotoxic chemotherapy and refractory to EGFR tyrosine kinase inhibitors.[4]

Sorafenib, a multitargeted tyrosine kinase inhibitor, inhibits among others the Ras-Raf pathway. In a recent large scale sequencing study, more than 1000 somatic mutations in 188 human lung adenocarcinomas were discovered. In this study, Sorafenib was suggested as potential treatment option.[5] Sorafenib has been evaluated in unselected advanced patients with NSCLC both as a single agent and in conjuncture with platinum doublet chemotherapy as first-line treatment. The results of these studies are not equivocal: although the single-agent studies showed some activity of sorafenib in all lines of treatment, the ESCAPE phase III trial failed to improve survival when sorafenib was added to the commonly used paclitaxel-carboplatin doublet. We hypothesized that selecting patients with NSCLC with K-Ras mutated tumors would enhance the clinical efficacy of sorafenib. Herein, we report our initial experience with this approach. This proof of concept study was approved by the Medical Ethical Committees of the two participating medical centers.

K-Ras mutation analyses was performed on DNA extracted from paraffin-embedded tumor tissue by manual dissection and overnight incubation with proteinase K. Subsequently, high-resolution melting and sequencing mutations were confirmed.[6] Ten patients with advanced NSCLC, progressive after at least one line of chemotherapy and harboring a K-Ras mutation were offered treatment with sorafenib 200 mg or 400 mg twice daily, which was administered until progression or unacceptable toxicity. Response was evaluated every 4 to 6 weeks by computed tomography scanning of the chest using RECIST criteria. Ten patients with a K-Ras mutation, 4 G12V, 4 G12C, 1 G12A, and 1 G13S including six women and four men with good performance status (1 performance status [PS] 0, 7 PS 1, and 2 PS 2) and mean age of 56 years (range 44–70) were treated. All patients were current or exsmokers and were pretreated with at least one chemotherapy regimen. Details on patient characteristics and response to previous chemotherapy regimen are provided in the Table 1.

The observed toxicity of treatment was not different from that previously reported in single-agent trials of sorafenib. The most troublesome toxicity consisted of hand-foot syndrome although this did not exceed grade 2. Three patients interrupted treatment for diarrhea grade II, depression, and infection in a cavitating tumor. Surprisingly, three partial remissions (PRs) and three minimal responses (MRs) 5 of which were associated with tumor cavitation were observed. The median progression-free survival was 3 months (95% CI: 2.2–3.8 months).

In our opinion, based on these results, further testing of sorafenib in phase II setting in treatment resistant K-Ras mutated NSCLC is warranted.

*Department of Pulmonary Diseases, Vrije Unversiteit Medical Centre, Amsterdam; †Department of Pulmonary Diseases, Maastricht University Medical Centre, Maastricht, The Netherlands; ‡Department of Pathology, Vrije Unversiteit Medical Centre, Amsterdam; and §Department of Pathology, Maastricht University Medical Centre, Maastricht, The Netherlands.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Egbert F. Smit, MD, PhD, Department of pulmonary diseases, Vrije Universiteit Medcial Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands. E-mail: ef.smit@vumc.nl

ISSN: 1556-0864/10/0505-0719

TABLE 1. Patient Characteristics and Response to Therapy

Sex	Age	PS	Stage	Hist.	*K-Ras* mut	Prior CT	Best Response	Response Sorafenib	PFS (mo)	Cavitation
M	70	1	IV	BAC	G12V	4 lines	MR	MR	3	+
F	48	2	IV	SSC	G12V	1 line	PD	PD	2	
M	70	1	IV	BAC	G12V	2 lines	PD	PR	8	+
F	44	1	IV	Adeno	G12C	1 line	PD	SD	3	
F	47	1	IV	Adeno	G12C	2 lines	SD	PR	5	
M	55	1	IV	LC	G13S	3 lines	PR	PR	6+	
F	62	0	IV	LC	G12V	4 lines	PR	MR	5	
F	54	1	IV	Adeno	G12A	2 lines	SD	MR	1.5	+
M	56	2	IV	Adeno	G12C	4 lines	Unknown	SD	2	+
F	61	1	IV	Adeno	G12C	3 lines	PD	SD	2.5	+

BAC, broncho alveolar cell carcinoma; CT, computed tomography; LC, large cell carcinoma; PD, progressive disease; PFS, progression-free survival; SCC, squamous cell carcinoma; SD, stable disease.

REFERENCES

1. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
3. Rodenhuis S, van de Wetering ML, Mooi WJ, et al. Mutational activation of the K-ras oncogene. A possible pathogenic factor for adenocarcinoma of the lung. *N Engl J Med* 1987;317:929–935.
4. Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic K-Ras mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small cell lung cancer and colorectal cancer. *Lancet Oncol* 2008;9:962–972.
5. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008;455:1069–1075.
6. Kramer D, Thunnissen FB, Gallegos-Ruiz MI, et al. A fast, sensitive and accurate high resolution melting (HRM) technology-based assay to screen for common K-Ras mutations. *Cell Oncol* 2009;31:161–167.