mutation in EGFR. *Nat Genet* 2005;37: 1315–1316.
5. Inukai M, Toyooka S, Ito S, et al. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. *Cancer Res* 2006;66:7854–7858.
6. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res* 2005;65:7568–7572.
7. Vikis H, Sato M, James M, et al. EGFR-T790M is a rare lung cancer susceptibility allele with enhanced kinase activity. *Cancer Res* 2007;67:4665–4670.

Complete Response of Recurrent Squamous Cell Carcinoma of the Lung: Dose the Dose Matter?

To the Editor:

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor and has shown significant clinical benefit in patients with various cancers.[1] A randomized phase II study comparing carboplatin plus paclitaxel with or without bevacizumab in non-small cell lung cancer patients demonstrated that the addition of bevacizumab results in an increase in time to disease progression.[2] However, because of an increased risk of pulmonary hemorrhage with bevacizumab treatment, a subsequent large phase III study excluded patients with squamous cell histology.[3] In this report, we present an elderly patient with recurrent squamous cell carcinoma of the lung who achieved complete response after treatment with bevacizumab plus carboplatin and paclitaxel without developing any hemorrhagic complications.

A 79-year-old man visited our hospital in July of 2007 with cough and sputum for a month. The patient underwent a left upper lobe lobectomy in May of 2005. Pathology revealed poorly differentiated squamous cell carcinoma, and was staged as T2N1M0. After surgery, four cycles of vinorelbine plus cisplatin adjuvant chemotherapy were administered.

Upon admission, his Eastern Cooperative Oncology Group (ECOG) performance status was 2. Chest computed tomography (CT) scan revealed recurrence of the disease in the left main bronchus involving the carina, and a large intraluminal-protruding mass formation with internal necrosis (Figure 1). Biopsy revealed a squamous cell carcinoma, pathologically confirming disease recurrence. Chemotherapy with bevacizumab 7.5 mg/kg combined with carboplatin, area under the curve 4, and paclitaxel 175 mg/m^2 was given once every 3 weeks for 4 cycles. CT scan after the second cycle showed complete response (Figure 2) without any evidence of pulmonary hemorrhage. The CT scan after the fourth cycle showed that complete remission was maintained. After completing the regimen, the patient has been receiving bevacizumab alone for an additional eight cycles without evidence of recurrence.

The efficacy of bevacizumab in angiogenesis inhibition in non-small cell lung cancer has already been documented,[3,4] but comes at a significant price; it is often associated with adverse side effects, including pulmonary hemorrhage, which may be a life-threatening condition. A randomized phase II study conducted by Johnson et al.[2] warned of the risk of bleeding in tumors of the squamous cell histology, tumors located close to major vessels, and tumors with necrosis or cativation. Thus, a phase III trial (ECOG 4599) of bevacizumab excluded patients with squamous cell histology, brain metastasis, or anticoagulation medications.[3]

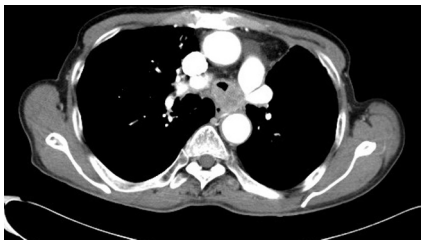

FIGURE 1. Computed tomography (CT) scan at the time of recurrence. Necrotic mass involved the posterior wall of the proximal left main bronchus. Biopsy was positive for recurrent squamous cell carcinoma.

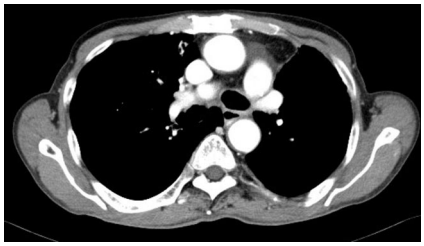

FIGURE 2. Computed tomography (CT) scan after the second cycle of bevacizumab, carboplatin, and paclitaxel chemotherapy. There was complete resolution of the necrotic mass involving the left main stem bronchus.

This is the first case report of an elderly patient with squamous cell histology who showed complete response after being treated by bevacizumab combined with carboplatin and paclitaxel. This finding is significant in that the patient had a higher risk for pulmonary hemorrhage because he was elderly, had poor performance status, and had squamous cell histology, which was centrally located and showed necrosis. A recent subset analysis of the ECOG 4599 trial revealed no survival benefits of bevacizumab plus caboplatin and paclitaxel for elderly patients (>70 years). This finding can be explained by the higher toxicity when adding bevacizumab to chemotherapy compared with chemotherapy alone.[5]

In our case, we used a lower dose of bevacizumab (7.5 mg/kg), and an attenuated dose of carboplatin (area under the curve 4) and paclitaxel (175 mg/m^2) compared with the ECOG 4599 trial.[3] It seems that an attenuated dose of chemotherapy and a lower dose of bevacizumab can reduce the complications and the toxicity. Further clinical studies will be warranted to determine whether bevacizumab is indeed a safe regimen in the management of squamous cell carcinoma of the lung and whether an attenuated dose plays an important role in elderly patients.

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REFERENCES

1. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005;23: 792–799.
2. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184–2191.
3. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
4. Cohen MH, Gootenberg J, Keegan P, et al. FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. *Oncologist* 2007;12:713–718.
5. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of eastern cooperative oncology group trial 4599. *J Clin Oncol* 2008;26:60–65.

Wood-Smoke Exposure (WSE) as a Predictor of Response and Survival in Erlotinib-Treated Non-small Cell Lung Cancer (NSCLC) Patients

To the Editor:

Coal and biomass serves as a major fuel source for >50% of the world's population.[1] In Colombia the prevalence of wood-smoke exposure (WSE) in areas having less economic development is around 24%. The amount of pollution due to wood-smoke (WS) is elevated; moreover, it has been calculated that cooking with wood for 3 h/d, exposes people to similar amounts of benzo-pyrene as smoking 3 packs of cigarettes/d.[1,2] This confirms, at least in part, that carcinogens present in WS are similar to those associated with tobacco. There is biologic plausibility for the association of WSE and non-small cell lung cancer because of a similar effect on p53, phospho-p53, and MDM2 protein expression as occurs in tobacco smokers.[3] Another's, have shown an abnormal GSTP-1 genotype, matrix metalloproteinase expression, and DNA adduct formation.[4]

In a previous issue of the JTO, Arrieta et al.[5] described the results of 42 non-small cell lung cancer patients who were being treated with erlotinib and had been exposed to WS for approximately 40 years; 14% of these subgroup patients had been smokers, overall response rate was 34% and clinical benefit was 67%. Histologic subtype and WSE were the variables positively influencing erlotinib response. The study also showed that the independent factor which most affected progression-free survival (PFS) and overall survival was WSE, and a mean of 17.6 and 19.2 months has being found for each of these outcomes, respectively. Nevertheless, response rate to erlotinib among smokers was strikingly high (19%), 16% of the subjects included had stage IIIB disease and PFS rate for patients with WSE curiously proved to be greater than in patients having epidermal growth factor receptor mutations. Mean follow-up time was short (4.5 months) and possible confusion variables (mutational profile, smoking history, comorbidity) were not suitably debugged.

These findings go against the scientific aphorisms used for predicting epidermal growth factor receptor-tyrosine kinase inhibitors response in patients suffering from lung adenocarcinoma, thereby supporting a theory regarding an alternative route for tumors being produced by WSE. The main outcomes in a series of 156 patients suffering from lung adenocarcinoma treated in Bogotá (Colombia) were analyzed in an attempt to ascertain the clinical findings and the biologic hypothesis advanced by Arrieta's group. Average age was 64 years, 53% were female, 39% had never been smokers, 24% had been considerably exposed to WS, and 23% of patients had received erlotinib during some stage of the disease. Nine of these subjects had been exposed to WS and 27 had not been. Seven patients having WSE had been smoking for an average of 14 years.

Overall response rate to erlotinib among patients with and without WSE was 5% and 47% ($p = 0.0023$), respectively. PFS was also significantly higher among patients who had no history of WSE and who had received erlotinib as first-line ($p = 0.037$) and second-line intervention ($p = 0.044$). Among patients having WSE history, overall survival was 6.6 months (5.8–7.3) for those treated with erlotinib and 15.4 months (10.7–20.1) for those not treated with this compound ($p = 0.0022$) (Figure 1). Such difference could be attributed to greater compromise of performance status in the group with WSE (61% Eastern Cooperative Oncology Group ≥2) due to the marked deterioration of pulmonary function.

In line with Arrieta's proposal, a multivariate analysis was carried out for determining the factors influencing mortality among patients with WSE. Only performance status ($p = 0.053$) and gender ($p = 0.044$) were seen to be significant. Our data did not support the findings described by Arrieta et al., highlighting the need for more consistent studies in this field to be carried out further.

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