brief communication

Preliminary experience with bevacizumab in combination with standard chemotherapeutic regimens in the treatment of non-small cell lung cancer: a retrospective study

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It is estimated that approximately 564,830 Americans died from cancer in 2006, corresponding to over 1500 deaths per day, with lung cancer being among the ten leading cancer types. A total of 1.2 million cancer deaths worldwide were attributed to lung cancer in 2002. Smoking mainly causes lung cancer; 95% of patients with lung cancer are smokers. The mortality is high, with a 5-year crude survival from 5% to 15%. One-quarter of the patients have small cell lung cancer and three quarters have non-small cell lung cancer (NSCLC), mainly squamous cell carcinoma, adenocarcinoma and large cell carcinoma.

Only a minority of patients with NSCLC are suitable candidates for radical curative treatment; the majority present with locally advanced or metastatic disease at diagnosis and can obtain only a modest survival benefit from palliative platinum-based chemotherapy with or without radiotherapy. The prognosis for such patients is poor, with 5-year survival rates of less than 10%. Median survival for patients with locally advanced disease or metastatic disease is 18 and 9 months, respectively. For first-line treatment of patients with unresectable advanced (Stage IIIb/IV) NSCLC, platinum-based doublets are standard. The introduction of third-generation cytotoxic agents (such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan) achieved improvements in tumor response and tolerability, but only modest improvements in survival, and it may be that chemotherapy has reached its maximum potential.

Recent therapies for NSCLC that are under intense development target novel cellular entities, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), which was originally discovered in the 1980s. VEGF is expressed in normal tissues, and in almost every type of human tumor. Its expression is seen in alveolar macrophages, normal bronchiolar and differentiated columnar epithelial cells. VEGF increases permeability by inducing endothelial fenestrations, thus allowing the leakage of plasma proteins into the extravascular tissue and promoting the creation of a fibrin-like microenvironment. This microenvironment serves as the foundation for neovascularization, tumor growth, propagation, and metastasis. Several studies indicate a correlation between VEGF expression, microvessel density (MVD) and poor prognosis in patients with NSCLC. Youn et al reported that a high VEGF level correlated with high MVD, short survival and early postoperative relapse. Ushijima et al found that high MVD values carried an especially poor prognosis when associated with a high expression of VEGF.

Bevacizumab (Avastin, F. Hoffmann-La Roche Ltd, Basel, Switzerland) is a recombinant humanized monoclonal antibody against VEGF. Preclinical in vivo models demonstrate that bevacizumab inhibits growth of a variety of human cancer cell lines in a dose-dependent manner. In addition, by eliminating excess VEGF, newly formed tumor vessels become less permeable, resulting in a reduction of interstitial pressure. It has been shown that the latter effect increases the diffusion of chemotherapeutic drugs in the tumor and perhaps potentiates their activity.

A randomized phaged II study suggested the benefit of adding bevacizumab to standard chemotherapy for advanced NSCLC. These results led to the incorporation of bevacizumab in the treatment of such patients at our institution when possible, before its final regulatory approval by the European authorities. Subsequently, the confirmatory phase III study was published, further...
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supporting our practice. We present hereby a retrospective analysis of the outcomes of our early cohort of NSCLC patients who received bevacizumab, aiming at better characterizing the feasibility, safety and efficacy of bevacizumab in such patients.

PATIENTS AND METHODS

The study population included male and female patients 18 years of age or older who had stage IIIB or IV, advanced or recurrent metastatic NSCLC, and had received a bevacizumab combination, on a compassionate basis, before its regulatory approval. The decision on the use of bevacizumab was based on clinical judgment and the permission for such a compassionate use by the Hellenic Drug Organization (the central regulatory agency). Patients who had received prior therapy with various chemotherapeutic regimens were included in the study; however, the majority of patients were chemotherapy naïve. There was no intentional exclusion of patients from receiving bevacizumab other than serious co-morbid conditions, according to clinical judgment and centrally located squamous cell cancer.

Good clinical practice standards applied to our cohort. Pretreatment evaluation included a complete medical history, physical examination and standard laboratory examinations (full blood count, biochemical profile, prothrombin time, international normalized ratio, and partial thromboplastin time). CT or MRI of the chest, abdomen and brain were taken, and performance status was assessed according to Eastern Cooperative Oncology Group (ECOG) guidelines. A complete blood count was obtained regularly. An interim medical history, physical examination, and the laboratory tests listed above were repeated prior to the start of each cycle of therapy. Tumor assessment with imaging was performed every 6 weeks while on therapy and every 8 weeks after completion; responses were determined by the investigators according to WHO criteria; stability required a minimum of 12 weeks.

Treatment plan

Every patient received bevacizumab 15 mg/kg on day 1 every 3 weeks, along with standard chemotherapeutic regimens including carboplatin/paclitaxel, carboplatin-pemetrexed, platinum with gemcitabine, docetaxel-based chemotherapy, and erlotinib. Because bevacizumab was not approved for NSCLC during the study period, it was commercially provided after communication with regulatory authorities and the patient’s insurance company. Its use was justified by existing clinical evidence, as the best available palliative treatment, on a compassionate basis.

Finally, growth factor was administered on a per-need basis and relatively liberally: 17 patients received leukocyte colony-stimulating factor at some point.

Statistical analysis

The primary objective of the study was to assess the impact of bevacizumab in combination with various chemotherapeutic regimens on patient outcomes in a preliminary manner. Main endpoints included the description of toxicity outcomes on all patients; secondary endpoints included the median overall (OS) and progression-free survival (PFS) rates and clinical response rates of patients receiving first-line treatment. Data are expressed as median and minimum-maximum for continuous variables and as percentages for categorical data. OS and PFS were estimated with the Kaplan-Meier product-limit method. All tests were two-sided with a 95% significance level. The statistical analysis was carried out using the statistical package SPSS version 15.00 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

The 20 patients with NSCLC treated at our department between April 2005 and August 2007 and reviewed for this study included 16 (80%) males and 4 (20%) females with a median age of 54.5 years (range, 35-75 years) (Table 1). The majority of patients had stage IV disease. All patients had confirmed adenocarcinoma of the lung with the exception of one patient who had relapsed after lobectomy with peripherally located squamous cell carcinoma and another who had adenoid cystic carcinoma. Due to local insurance restrictions, procurement of bevacizumab was feasible for approximately one quarter of the otherwise eligible patients who visited our clinic.

At therapy initiation, 17 patients (85%) were chemotherapy naïve and therefore on first-line treatment. The remaining 3 patients (15%) were on second-line treatment. In addition to bevacizumab, 9 patients (45%) received a chemotherapeutic combination of carboplatin/paclitaxel, 3 patients (15%) a combination of carboplatin/pemetrexed, 3 patients (15%) received docetaxel-based chemotherapy, 2 patients (10%) received a combination of platinum/gemcitabine, 1 patient (5%) received a combination of carboplatin/gemcitabine, 1 patient (5%) received erlotinib, and 1 patient (5%) received a combination of cetuximab/irinotecan. Three patients (15%) had an ECOG performance status (PS) of 0, 11 patients (55%) had a PS of 1, 5 patients (25%) had a PS of 2 and 1 patient...
(5%) had a PS of 3. For all treated patients, the median number of therapy cycles administered was 6 (range, 1-18). The median follow-up of this cohort was 6.1 months (range, 1-26).

**Toxicity**

In general, bevacizumab was well tolerated by most patients. No thrombotic events were noted. Grade 2 hypertension occurred in 3 patients. Uncomplicated
epistaxis was reported in 5 patients and one patient developed mild gingival bleeding. There were no episodes of febrile neutropenia or proteinuria (Table 2). Overall, serious toxicity possibly related to bevacizumab administration was observed in one case.

Response, overall survival and progression free survival rates
Of the 17 patients on first-line treatment, 2 patients (11.8%) achieved a complete response and 6 patients (35.3%) achieved a partial response (overall response rate, 47.1%). Stable disease was observed in 6 patients (35.3%) and 1 patient (5.9%) progressed (Table 3). The 1-year overall survival rate was 52.4% and the median OS was 14 months (range, 4.8-23.2 months) (Table 4, Figure 1). The 12-month PFS rate was 48.8% and the median PFS was 10.2 months (range, 4.3-16.1 months) (Table 4, Figure 2).

DISCUSSION
The benefit of adding bevacizumab to standard treatment for unresectable NSCLC is by now well documented. In E4599, a phase III study of bevacizumab in NSCLC, Sandler et al showed that the median overall survival was 12.3 months in the group of patients who received paclitaxel-carboplatin-bevacizumab, as compared to 10.3 months in the paclitaxel-carboplatin group ($P=.003$). Survival rates were 51% in the paclitaxel-carboplatin-bevacizumab group as compared to 44% in the paclitaxel-carboplatin group at 1 year and 23%, as compared to 15%, respectively, at 2 years. The median PFS was also significantly improved in the paclitaxel-carboplatin-bevacizumab group (6.2 months, as compared with 4.5 months in the paclitaxel-carboplatin group). Among 773 patients with measurable disease, the addition of bevacizumab to paclitaxel and carboplatin improved the response rate; 59 of 392 patients (15%) in the paclitaxel-carboplatin group had a response, as compared with 133 of 381 patients (35%) in the paclitaxel-carboplatin-bevacizumab group ($P<.001$).

In another randomized, phase II trial by Johnson and associates comparing carboplatin and paclitaxel with or without bevacizumab at two dose levels (7.5 mg/kg versus 15mg mg/kg) in 99 patients with untreated advanced or metastatic non-small cell lung cancer, higher response rates (31.5% versus 18.8%), longer median time to progression (7.4 versus 4.2 months, $P=.023$), and longer survival (17.7 versus 14.9 months, $P=.63$) were demonstrated in patients receiving the higher-dose (15 mg/kg) bevacizumab. A total of 19 patients originally receiving placebo with chemotherapy...
were crossed over to bevacizumab at the time of disease progression, with a 1-year survival rate of 47%.\textsuperscript{28,29}

The results of our uncontrolled and retrospective analysis of the compassionate use of bevacizumab in a cohort of patients with advanced NSCLC treated at our institution are consistent with the above-described benefit of bevacizumab in this population. The observed overall survival is in line with the report of the randomized phase III study while the response rate observed is extremely encouraging and exceeds expectations. In addition, the durability of responses and the overall deceleration of the expected pace of the disease are particularly rewarding, and in retrospect justified the enthusiasm regarding the initiative to use bevacizumab regimens in our patients, before its regulatory approval. Apparently, this therapeutic option was facilitated by the experience of our center and our investigators in the use of bevacizumab in colon cancer patients, over the last 4 years.

Our study results are limited by the relatively small number of patients who received off-label bevacizumab therapy for the treatment of NSCLC; thus any conclusions should be drawn with caution. Nevertheless, our study illustrates a preliminary experience in patients with lung cancer, in a real world clinical setting, outside the rigor and beyond the limitations of a restricted trial design. In fact, several of our patients would have been eliminated from clinical studies. Regarding the safety aspect of the regimen studied, our experience demonstrated a toxicity profile that did not diverge from the expected. In particular, although bevacizumab was previously reported to increase the rate of neutropenia, there was no neutropenic complication in our cohort. This was certainly facilitated by the use of growth factors, according to the judgment of the treating physician. In addition, the incidence of hypertension was low and this complication was relatively easily managed.

It is also noteworthy that one case of fatal pulmonary hemorrhage occurred several months after bevacizumab discontinuation, and is of unclear causal relationship with its administration. That patient had suffered many complications and had received mediastinal irradiation at a site of a recent infection, notwithstanding the presence of a foreign body, namely an esophageal stent. Fatal hemorrhages may occur in patients with lung cancer, even without the use of bevacizumab. Although the fatal hemorrhage may have not been related to bevacizumab per se, the development of the tracheoesophageal fistula on the basis of a pulmonary abscess may well be related. The proper healing of the esophageal wall adjacent to the abscess may have been impaired by the circulating bevacizumab and may have led to the formation of the fistula. Such a patient with centrally located lesions adjacent to major vessels might have been eliminated from certain clinical studies such as the AVAIL study, but he would have been included in the ECOG study. Nevertheless, despite concerns over pulmonary hemorrhage in patients receiving bevacizumab in the E4599 study,\textsuperscript{27} no statistically significant difference in pulmonary hemorrhage between the two arms was proven.

Despite the unfortunate outcome of the one patient described, the addition of bevacizumab to standard chemotherapeutic regimens was otherwise well tolerated and appeared to yield highly beneficial outcomes for this cohort of patients. Thus, our experience is in agreement with the reports of previously conducted prospective studies, encouraging us to continue the use of bevacizumab in the adjuvant setting, in patients with non-squamous, NSCLC. Nevertheless, confirmatory evidence from future well-designed trials is warranted to precisely elucidate the beneficial role of bevacizumab in NSCLC.
REFERENCES