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ORIGINAL RESEARCH

Potential Antiangiogenic Treatment Eligibility of Patients with Squamous Non-Small–Cell Lung Cancer: EPISQUAMAB Study (GFPC 2015-01)

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On behalf of the French Lung Cancer Group

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Background: Antiangiogenic agents have improved the prognosis of non-squamous non-small–cell lung cancers (NSCLCs), even though all the patients are not eligible to receive them because of counterindications linked to the tumor's characteristics or comorbidities. Much less information is available about the eligibility of patients with squamous non-small–cell lung cancers (SQ-NSCLCs) to receive antivascular endothelial growth-factor (VEGF) treatments, even though such molecules are being developed for this histology. This study was undertaken to determine the percentage of advanced SQ-NSCLC patients who would be eligible to receive an antiVEGF agent as second-line systemic therapy.

Methods: This observational, multicenter, prospective study evaluated advanced SQ-NSCLC patients' criteria for ineligibility to receive an antiVEGF during a multidisciplinary meeting to choose their standard second-line systemic therapy.

Results: Among the 317 patients included, 53.6% had at least one ineligibility criterion, and ~20% had at least two, with disease extension to large vessels (39.8%), tumor cavitation (20.5%), cardiovascular disease (11%) and/or hemoptysis (7.2%) being the most frequent. Patients with an ECOG performance score of 1/2 had more cardiovascular contraindications that those with scores of 0.

Conclusion: Almost half of the SQ-NSCLC patients included in this study would have been eligible to receive an antiVEGF agent. The development of these molecules for these indications should be encouraged.

Keywords: lung cancer, squamous non-small cell, antiangiogenic treatments

Introduction

Lung cancer is the first cause of cancer deaths of men and women in the United States,[1] with a 5-year survival rate of ~16%.[2,3] Lung cancers are separated into two major categories based on histology, clinical management and prognosis: non-small–cell lung cancer (NSCLC) and small-cell lung cancer (SCLC).[3] NSCLCs represent more than 85% of these tumors.[4] Its two major histologies are non-squamous and squamous (SQ) carcinomas, with the latter representing 30% of NSCLCs.[4] NSCLC outcomes changed remarkably during the early 2000s, particularly for advanced lung adenocarcinomas.[4] Those changes reflect the development of new agents devoted to specific oncological drivers: inhibitors of epidermal growth factor-receptor (EGFR), anaplastic lymphoma kinase (ALK) and vascular endothelial growth factor (VEGF), and finally immunotherapy.[5,6] However, median survival time was not prolonged for SQ-NSCLCs.[7] The difference between the two subtypes may

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be due to a modest effect against SQ-NSCLCs of the agents used to treat adenocarcinomas.[8,9] Therefore, immune-checkpoint inhibitors (ICIs) for SQ-NSCLCs, developed after those for non-squamous NSCLCs, could modify their prognoses.[10]

Because angiogenesis is a pejorative factor for several tumors, inhibiting proangiogenic factors represents a potential avenue for therapeutic development.[9] While the role of VEGF in angiogenesis is well established,[9,11,12] studies on SQ-NSCLCs have been limited[9,11–13] by concerns about life-threatening pulmonary hemorrhage[14,15] and guidelines excluded these patients from the indication.[16]

Bevacizumab (BVZ) was the first agent targeting VEGF to prolong survival when combined with chemotherapy for selected NSCLC patients.[6,14] Despite BVZ's demonstrated efficacy in phase II and III trials on NSCLC patients,[5,9] adverse events like significant bleeding, including major hemoptysis, delayed its development for SQ-NSCLC patients.[15,16]

Tolerability of BVZ in combination with chemotherapy was established in a phase I trial on all NSCLC subtypes.[17] In an early phase II trial of BVZ for NSCLC patients,[18] among six patients experiencing life-threatening pulmonary hemorrhages, four had SQ-NSCLCs; four of the six patients died. Pertinently, all six patients had centrally located tumors close to major blood vessels and five had cavitation or necrosis. Results of observational studies confirmed BVZ safety[11,12] and excluded certain initial contraindications, like brain metastases. Multiple trials have evaluated BVZ as second-line therapy. In the phase III ULTIMATE trial,[19] 166 patients with advanced NSCLCs progressing after first- or second-line therapy were randomized to receive weekly the paclitaxel–BVZ combination compared to docetaxel; progression-free survival (PFS) was significantly longer for the former group but overall survival (OS) was comparable for the two groups.

New agents with antiVEGF activity have been developed for SQ-NSCLCs.[20] A phase III trial that included 1253 randomized patients (all NSCLC histology, 25% SQ-NSCLCs) compared docetaxel (75 mg/m^2) in combination with ramucirumab (10 mg/kg) or placebo.[21] Ramucirumab adjunction to docetaxel was associated with significantly prolonged PFS and OS. That OS benefit was also retained for the SQ-NSCLC subgroup (respective median OS, 9.5 vs 8.2 months).[22] Those results led to the US Food and Drug Administration and European Medicines Agency approvals of ramucirumab for both NSCLC histologies.

Nintedanib, a multitarget antiangiogenic agent, was evaluated in combination with docetaxel in a large phase III randomized trial,[9,23] comparing docetaxel to placebo for all NSCLC histological subtypes. Significantly improved OS rates were obtained for patients randomized to receive docetaxel and nintedanib vs placebo: those whose adenocarcinomas progressed within medians of 10.9 vs 7.9 months, respectively, and for the entire adenocarcinoma subset (12.6 vs 10.3 months). However, the entire study population did not benefit from OS prolongation. The European Medicines Agency—but neither the US Food and Drug Administration nor Health Canada—approved nintedanib to treat non-squamous NSCLCs.

However, few real-life data from SQ-NSCLC patients are available.

This study was undertaken to assess prospectively the clinical and radiological characteristics of advanced SQ-NSCLC patients about to receive second-line therapy to determine the percentage of them who would have been eligible to receive antiVEGF therapy.

Methods

This observational, multicenter, prospective study included consecutive advanced SQ-NSCLC patients >18 years old, whose disease progressed after first-line chemotherapy, and evaluated their criteria rendering them ineligible to receive an antiangiogenic treatment. That evaluation was carried out in each center, at the time of multidisciplinary meetings to choose their standard second-line systemic regimen.

The following information was collected: Eastern Cooperative Oncology Group performance status (ECOG PS); lung cancer characteristics: histology, TNM grade, stage, number and type of metastases; and first- and second-line treatments.

The criteria retained for ineligibility to receive an antiVEGF were: tumor with central cavitation; tumor extension to a large vessel, with a 180° branching angle; hemoptysis >3 mL during the previous 3 months; prior thromboembolic events, myocardial infarction, unstable angina, stroke, transient ischemic attack during the preceding 6 months; uncontrolled hypertension >150/90 mm Hg; grade-3/4 hemorrhagic disorder, vasculitis or gastrointestinal bleeding; gastrointestinal perforation or digestive tract fistula during the previous 6 months; inflammatory bowel disease, digestive tract obstructions or intestinal resection, Crohn's disease, ulcerative colitis or chronic diarrhea.

Data were analyzed with Excel software (version 16.16.10, Microsoft 2018).

The Ethics Committee of Limoges University Hospital approved the protocol for this observational study on

December 12, 2015. All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Results

From July 2016 to July 2017, 40 centers included 317 patients: 256 (80.8%) men; most in good general condition (ECOG PS 0/1: 82.0%); only 3.5% were non-smokers; and 65.3% had metastatic SQ-NSCLCs at diagnosis (Table 1). All patients had received first-line chemotherapy. As second-line therapy, 82% received chemotherapy, 7% were given a tyrosine-kinase inhibitor and radiotherapy was prescribed for 11%.

Table 1 Characteristics of the 317 Advanced SQ-NSCLC Patients Evaluated for Eligibility to Receive Anti-VEGF Therapy

Characteristic	Value
Age, median (range), years	68 (32–89)
Sex	
Male	255 (80.4)
Female	62 (19.6)
ECOG PS (diagnosis)	
0	94 (29.7)
1	166 (52.4)
≥2	46 (14.5)
Unknown	11 (3.5)
Smoking status	
Smoker	160 (50.5)
Ex-smoker	138 (43.5)
Non-smoker	11 (3.5)
Unknown	8 (2.5)
Stage at diagnosis	
Non-metastatic	110 (34.7)
IV	207 (65.3)
Number of metastatic sites	
1	125 (60.4)
≥1	82 (39.4)
Metastatic site	
Brain	25 (7.9)
Nodes	18 (5.7)
Lung	83 (26.2)
Liver	34 (10.7)
Adrenal gland	27 (8.5)
Bone	63 (19.9)
Skin	3 (0.9)
Other(s)	64 (20.2)

Note: Results are expressed as number (%), unless stated otherwise.
Abbreviations: SQ-NSCLC, squamous non-small–cell lung cancer; VEGF, vascular endothelial growth factor; ECOG PS, Eastern Cooperative Oncology Group performance status.

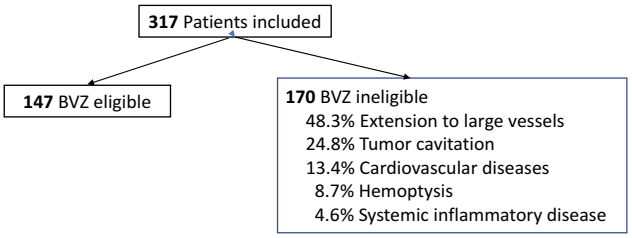

Figure 1 Flow chart of the study. Patients could have more than 1 ineligibility criterion.

The VEGF-eligibility evaluation found that 53.6% of the patients had an ineligibility criterion and 20% had at least two (Figure 1, Table 2).

Table 3 reports the distributions of certain characteristics of these SQ-NSCLC patients, according to the main antiVEGF ineligibility criteria: tumor cavitation, extension to large vessels, hemoptysis, cardiovascular diseases.

Discussion

The results of this novel, observational evaluation of previously unassessed eligibility of advanced SQ-NSCLC patients to receive a second-line antiangiogenic agent showed that slightly less than half were eligible. Based on the more abundant data available on non-squamous NSCLC patients, about 20–30% of them were ineligible.[4,6] No study on such patients has yet been published. Our results and conclusions have to be confirmed by prospective studies.

According to the rates of central lesions and large-vessel extensions, it is not surprising that a higher percentage of these patients were ineligible. In the REVEL trial,[22] 219 (26.6%) of the 825 screened patients did not meet inclusion criteria, knowing that patients with ECOG PS=2 and those with brain metastases were excluded; only 13% had large-vessel involvement and 10% had comorbidities. To help guide physicians' use of BVZ to treat NSCLC patients, an expert panel reviewed the available

Table 2 Reasons for Ineligibility of Advanced SQ-NSCLC Patients to Receive Antiangiogenics*

Reason for Ineligibility	Number (%)
Extension to large blood vessels	105 (48.3)
Tumor with cavitation	54 (24.8)
Cardiovascular disease†	29 (13.4)
Hemoptysis	19 (8.7)
Systemic inflammatory disease‡	10 (4.6)

Notes: *Patients could have several ineligibility criteria (n=217). †Prior thromboembolic event(s), uncontrolled hypertension, etc. ‡Hemorrhagic disorder, prior gastrointestinal perforation, systemic disease, inflammatory bowel disease, vasculitis.
Abbreviation: SQ-NSCLC, squamous non-small–cell lung cancer.

Table 3 Percentages of Clinical Factors as a Function of Ineligibility Criteria

Clinical Factor	Ineligibility Criterion			
	Extension to Large Vessels n=105	Cavitation n=54	Hemoptysis n=19	CV Diseases n=29
Men/women	81.9/18.1	77.8/22.2	89.5/10.5	93.1/6.9
Stage IV/others	65.7/34.3	75.9/24.1	63.2/36.8	72.4/27.6
>1/≤1 metastatic site(s)	60.9/39/1	65.9/34.1	58.3/41.7	71.4/28.6
1st-line chemotherapy	99.1	100	94.7	100
ECOG PS: 0/1;2;≥2	30.7;55.4;13.9	28.3;52.8;18.9	31.6;47.4;21.1	17.9;67.9;14.3

Abbreviations: CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status.

data to identify factors predictive of pulmonary hemoptysis and concluded that large blood-vessel infiltration might do so; however, no consensus has been established to define radiological infiltration. Eligibility for BVZ use is not affected by patient age, ECOG PS, or anticoagulation or antiplatelet therapy. All NSCLC patients for whom antiVEGF therapy is being considered should undergo individualized risk-benefit assessments.[24]

This study had several limitations. First, it was observational. It also relied on multidisciplinary meetings in each center and the usual practices of the radiologists and investigators in each center, which could have engendered some heterogeneity and modified the final results. However, the findings confirmed that almost one out of two advanced SQ-NSCLC patients was, indeed, eligible for antiVEGF therapy. Notably, eligibility evaluation is often difficult and observer-dependent, especially for the radiological criteria of vessel invasion of tumors. Those criteria were assessed by chest computed-tomography scans for eligibility to receive BVZ in an analysis of NSCLC patients with centrally located tumors;[25] discordance for eligibility was found for 55% patients. While interobserver strength of agreement was fair-to-moderate (mean kappa: 0.40), intraobserver strength of agreement was good-to-very-good (mean kappa: 0.74). Multivariate analysis retained the risk of discrepancy as essentially reflecting the assessment of contact between the tumor and vessels. Second, we did not collect the outcomes, particularly survival, as it was not the objective of the study.

Literature data are very scarce. The large majority of papers are limited to non-squamous NSCLCs.[26] Two recent studies reported real-life information about patients treated with angiogenesis inhibitors. For Nadler et al,[27] 13% received first-line BVZ, but none for the second line. For Armochalam et al,[28] in a large study (n=2899), BVZ was used only as second-line therapy for non-squamous NSCLC patients: BVZ alone for 2.7%, combined with pemetrexed or docetaxel for 4.8%, a platin doublet for 6.2%, or carboplatin–paclitaxel–atezolizumab for 6.9%.

The risk of bleeding did not stop further investigation of an antiangiogenic effect in SQ-NCLC patients.[29–32] A phase II trial on SQ-NSCLC patients evaluated targeting the VEGF pathway with axitinib, a novel pan-VEGF-receptor (R) inhibitor (e.g., inhibitor of all three: VEGFR-1, −2 and −3) and compared it to standard first-line cisplatin–gemcitabine regimen.[24] Experimental arm patients reached a median PFS of 6.2 months and a median OS of 14.2 months. The most frequent grade-≥3 toxicities were neutropenia (13.2%) and hypertension (13.2%), with only three (7.9%) patients experiencing hemoptysis, which was fatal for one (2.6%).[30]

More recently, several studies used a strategy to limit and closely monitor toxicity, and reexamined the potential of BVZ to treat SQ-NSCLCs. In the BRIDGE trial,[33] a new, sequential administration regimen of chemotherapy and BVZ was applied in an attempt to minimize BVZ toxicity in SQ-NSCLC patients. In that study, patients received two carboplatin–paclitaxel cycles, followed by that combination and BVZ for cycles 3–6, then BVZ maintenance alone, until progression or toxicity. Grade-3 pulmonary hemorrhage occurred in 1/31 (3.2% [95% confidence interval, 0.3–-13.5%]) patients; PFS was 6.2 months. While the pulmonary hemorrhage rate was lower than that reported in the phase II study described above,[18] using BVZ to treat SQ-NSCLCs remains investigational.[34,35]

That positive outcome encourages continuing studies on SQ-NSCLC patients and their combination in the near future with immune-checkpoint inhibitors ICIs.[36] ICIs will modify the use of these molecules. Hakozaki et al[37] showed that BVZ could increase the eligibility rate by 20% (paclitaxel–carboplatin–atezomizumab–BVZ combination) for *EGFR*-mutated NSCLCs that had received first-line tyrosine-kinase inhibitors. Angiogenesis inhibitors could have an immunosuppressive action;[38] in a small number of patients (16 adenocarcinomas

and 3 SQ-NSCLCs), the disease-control rate was 90% with the ramucirumab–docetaxel combination after nivolumab. BVZ and other antiangiogenics could be included in the global therapeutic strategy for metastatic SQ-NSCLCs.

Abbreviations

NSCLC, non-small–cell lung cancer; SQ-NSCLC, squamous NSCLC; BVZ, bevacizumab; VEGF, vascular endothelial growth factor; EGFR, endothelial growth-factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status.

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