Antiangiogenesis in Small-Cell Lung Cancer: Is There a Path Forward?


Study Overview

Objective. To evaluate efficacy of adding bevacizumab to first-line chemotherapy for treatment of extensive-disease small-cell lung cancer (ED-SCLC).

Design. Phase III prospective multicenter randomized clinical trial.

Setting and participants. The study was conducted at 29 Italian centers and was supported by the Agenzia Italiana del Farmaco. Study entry was limited to patients with histologically or cytologically documented ED-SCLC who were previously untreated with systemic therapy, were 18 years of age or older, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. Adequate bone marrow, renal, and liver functions were required. Patients with asymptomatic, treated brain metastases were eligible for trial participation. Exclusions included the following: mixed histologic diagnosis of SCLC and non–SCLC; history of grade 2 hemoptysis; evidence of lung tumor cavitation; significant traumatic injury within the 4 weeks before first dose of study treatment; other active malignancies (previous or current); and any underlying medical condition that might be aggravated by treatment.

Intervention. Patients received a combination of intravenous cisplatin (25 mg/m² on days 1 to 3), etoposide (100 mg/m² on days 1 to 3), and bevacizumab (7.5 mg/kg intravenously on day 1) administered every 3 weeks (experimental arm); or the same cisplatin and etoposide chemotherapy regimen alone given every 3 weeks (control arm). Carboplatin (area under the curve 5 on day 1) could be substituted for cisplatin in case of cisplatin contraindications or cisplatin-associated toxicity. Tumor response, on the basis of investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), was evaluated every 3 cycles during chemotherapy treatment. After 6 cycles of chemotherapy, tumor assessment was performed every 9 weeks in both arms. In the absence of progression, patients in the treatment arm continued bevacizumab alone until disease progression or for a maximum of 18 courses. Survival follow-up information was collected every 6 months after treatment termination or last dose of study drug, until death or loss to follow-up.
Main outcome measure. The primary end point was overall survival (OS). Response rate, toxicity, and progression-free survival (PFS) were secondary end points.

Main results. 205 patients were randomized between November 2009 and October 2015. 204 patients were considered in the intent-to-treat analysis (103 in the control arm and 101 in the treatment arm). Most patients were male with ECOG PS of 0 to 1. Median age was 64 years. The median number of chemotherapy courses administered was 6 in both arms. Cisplatin was used in majority of the patients. Average relative dose intensities for all drugs were well balanced between 2 groups. A lower percentage of patients in the treatment arm (14.7%) than in the control arm (22.3%) discontinued treatment because of radiologic disease progression, which was the main reason for treatment discontinuation.

At a median follow-up of 34.9 months, the median PFS was 5.7 in the control arm and 6.7 months in the treatment arm (hazard ratio [HR], 0.72; 95% CI, 0.54 to 0.97; \(P = 0.30\)). Median OS times were 8.9 months and 9.8 months, and 1-year survival rates were 25% and 37% (HR, 0.78; 95% CI, 0.58 to 1.06; \(P = 0.113\)) in the control arm and treatment arm, respectively. A significant effect of the maintenance treatment on OS (HR, 0.60; 95% CI, 0.40 to 0.91, \(P = 0.011\)) was observed. A subgroup analysis revealed a statistically significant interaction for OS between treatment and sex; the addition of bevacizumab led to a significant survival benefit in men (HR, 0.55) and to a possible detrimental effect in women (HR, 1.55; interaction test, \(P = 0.003\)).

Addition of bevacizumab did not result in increase in hematologic toxicity such as anemia, neutropenia, or thrombocytopenia. Concerning the nonhematologic toxicity, only hypertension was more frequent in the bevacizumab arm (6.3%) compared to chemotherapy alone arm (1%). The rates of proteinuria and thrombosis were similar in both arms.

Conclusion. The addition of bevacizumab to cisplatin and etoposide in the first-line treatment of ED-SCLC had an acceptable toxicity profile and led to a statistically significant improvement in PFS, which, however, did not translate into a statistically significant increase in OS.

Commentary

SCLC currently accounts for approximately 12% to 15% of all lung cancers [1]. It is characterized by a rapid growth rate, metastasis at the time of diagnosis, sensitivity to first-line platinum-based chemotherapy, and invariable recurrence and progressive resistance to subsequent lines of therapy. A number of clinical trials over the past 2 decades have failed to produce outcomes superior to platinum-based doublet chemotherapy, leaving a significant unmet need [2]. Vascular endothelial growth factor (VEGF) is the most important proangiogenic factor, and it is implicated in tumor growth [3]. Bevacizumab, a humanized monoclonal antibody directed against VEGF, is now indicated in the treatment of several tumor types including non–SCLC and breast, colorectal, kidney, and ovarian cancer. Positive signal with bevacizumab was seen in phase II studies, providing rationale for this phase III trial [4,5].

The study by Tiseo and colleagues reported the outcomes of a randomized study that added bevacizumab to standard combination therapy with platinum and etoposide for the treatment of ED-SCLC. A small statistically significant improvement was seen in PFS (6.7 months vs. 5.7 months, favoring the bevacizumab group). However, the study failed to meet the primary end point of improved OS.

So where do antiangiogenesis agents go from here? Alternative angiogenesis inhibitors with broader mechanism of action are being explored in clinical trials. One such trial (ClinicalTrials.gov identifier: NCT02945852) is evaluating the role of the tyrosine kinase inhibitor apatinib in combination with chemotherapy in ED-SCLC. Apatinib selectively inhibits the vascular growth factor receptor-2 (VEGFR2). In addition, this agent also inhibits c-kit and c-SRC tyrosine kinase. It would be interesting to see if antiangiogenic agents with broader mechanisms would be more effective in SCLC. Immuno-therapy with checkpoint inhibitors such as nivolumab and pembrolizumab have revolutionized the lung cancer treatment paradigm. It would be interesting to see if bevacizumab could be safely added to these immunotherapy agents. The ongoing CheckMate 370 (ClinicalTrials.gov identifier: NCT02574078) is addressing this question, evaluating the safety of combining nivolumab with bevacizumab in non-SCLC.

Applications for Clinical Practice

The current study does not support the addition of bevacizumab as a standard therapeutic option in the first-line treatment of ED-SCLC. However, given that there was a trend towards improved OS, alternative strategies of
incorporating antiangiogenesis agents should be considered in future clinical trials.

—Deval Rajyaguru, MD

References

Vigorous Physical Activity Associated with Greater Arterial Compliance in Both Large and Small Arteries


Study Overview

Objective. To investigate the association between habitually high levels of physical activity and the compliance of the large and small arteries in men and women throughout the life span.

Design. Cross-sectional study.

Setting and participants. 83 healthy men (n = 44) and women (n = 39) aged between 18 and 78 years were recruited to participate in the study. Potential participants were recruited via flyers designed to elicit responses from either very highly active (participate in regular, vigorous exercise more than 5 times per week) or less active/sedentary individuals (participate in light to moderate exercise less than 3 times per week or none at all). Both groups subjectively reported maintaining the specified activity level for at least the past 5 years. The highly active subjects performed regular vigorous swimming as their primary mode of exercise training as most were members of a varsity or masters swim team. All subjects were free of overt chronic diseases, nonsmokers, and none were taking vasoactive medications as assessed by a medical history questionnaire. All subjects provided written informed consent to participate. The study was reviewed and approved by the institutional review board at Indiana University.

Physical activity was self-assessed in all subject groups with a log detailing their activity over the previous 7 days. To ensure the older highly active population performed vigorous physical activity ≥ 5 days per week, the subjective activity log was verified by a 7-day previously validated, commercially available heart rate monitor and accelerometer (Actiheart, CamNtech, Cambridge, UK).

Main outcome measure. Compliance of the small and large arteries (inverse of stiffness) measured using a commercial pulse wave analyzer (Model CR-2000, Hypertension Diagnostics, Eagen, MN), which according to the manufacturer measures proximal capacitive compliance (C1, or estimate of large artery compliance) and distal oscillatory compliance (C2, or small artery compliance) [1].

Results. The study found a positive association between routine vigorous physical activity and arterial compliance. Specifically, the results suggest that vigorous physical activity is associated with greater compliance of the small and large arteries in both younger and older adults (P < 0.05). In addition, both the highly active and less active younger groups as well as the highly active older group demonstrated greater large arterial compliance compared to the less active older group (P < 0.008). No significant differences were found between men and women.
Conclusion. Researchers concluded that participation in habitual vigorous physical activity is associated with benefits to the compliance of the small and large arteries. Habitual vigorous physical activity over time may attenuate age-associated cardiovascular impairments.

Commentary
Arterial compliance declines with age, and increased arterial stiffness is associated with an increased risk of cardiovascular events [2]. Evidence suggests that physical activity may delay or prevent age-related increases in arterial stiffness [3]. Previous research regarding age-related arterial stiffness and exercise has focused primarily on the large arteries. For example, Tanaka found that regular aerobic-endurance exercise attenuates age-related reductions in central arterial compliance and restores levels in previously sedentary healthy middle-aged and older men [3]. More recently, a study by Duprez [4] found that small artery elasticity was superior to large artery elasticity with regard to predicting future CHD, stroke, and heart failure.

In this study, researchers cross-sectionally investigated the relationship of intense and continuous physical activity in young and older adults. The form of vigorous activity in this study was competitive swimming, as participants were recruited from a collegiate varsity and masters swim team. The study found a statistically strong association between routine vigorous physical activity and arterial compliance. These findings agree with several studies showing the benefits of vigorous exercise, but go beyond these by presenting findings on small artery compliance.

Methodologically, this study has some limitations. With the small sample, the study may not have been adequately powered. Further, physical activity assessment was by self-report in the main. Even though researchers had the participants keep a log, self-report measures may be inaccurate. Another limitation was the indirect method of measuring compliance, in which the radial waveform is calibrated to brachial blood pressure values. However, the researchers followed a valid model using the same BP level–based procedures reported in previous studies [1].

Applications for Clinical Practice
CVD is a major cause of disability and mortality in the United States. Health care professionals have a significant role to play in reducing cardiovascular risk factors in their patients, including encouraging aerobic exercise. The American Heart Association recommends at least 30 minutes of moderate-intensity aerobic activity at least 5 days per week or at least 25 minutes of vigorous aerobic activity at least 3 days per week, or a combination of moderate- and vigorous-intensity aerobic activity [4]. Patients can also be reminded that even modest levels of physical activity are associated with health benefits.

—Paloma Cesar de Sales, BS, RN, MS

References