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STUDY PROTOCOL

Efficacy and safety of bevacizumab in advanced lung adenocarcinoma patients with stable disease after two cycles of first-line chemotherapy: A multicenter prospective cohort study

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Abstract

Bevacizumab is the first antiangiogenetic monoclonal antibody, combined with platinum-based double agent chemotherapy, which has been reported to improve the objective response rate (ORR) and progression-free survival (PFS) in patients with advanced nonsquamous non-small cell lung cancer (NSCLC), and to improve overall survival (OS) in patients when combined with carboplatin and paclitaxel. However, serious adverse effects have been reported to be associated with bevacizumab therapy. In this multicenter prospective cohort study of advanced lung adenocarcinoma patients with stable disease after two cycles of platinum-based double agent chemotherapy, we will compare the ORR between the group who continued with their original chemotherapy regimen and the group in which bevacizumab was added to the original regimen. It is expected that there will be an ORR improvement of 20% in patients in the bevacizumab group plus chemotherapy, compared with those in the original chemotherapy group. This study has been registered as Clinical Trial NCT03240549.

Introduction

Lung cancer is one of the most common malignant tumors and the leading cause of cancer death worldwide and in China,[1, 2] of which non-small cell lung cancer (NSCLC) accounts for about 80%–85% by pathological type. The median overall survival (OS) is 8–10 months and the objective response rate (ORR) is 25%–35% in patients who have undergone treatment with traditional platinum-based chemotherapy plus third-generation agents.[3] First-line tyrosine kinase inhibitors (TKIs) have been reported to improve the prognosis of advanced NSCLC patients with active mutation of epidermal growth factor receptor (EGFR), or the echinoderm microtubule-associated protein like 4–anaplastic lymphoma kinase (EML4-ALK) fusion,[4, 5]

but platinum-based double agent chemotherapy is the first choice for patients with wild-type mutation and those patients in whom disease has progressed after therapy with one or more TKIs.

In a phase III study, cisplatin and pemetrexed demonstrated similar efficacy compared with cisplatin and gemcitabine in patients with advanced NSCLC; however, in the prespecified subgroup analysis, a significant improvement in OS was observed with cisplatin and pemetrexed in patients with nonsquamous NSCLC.[6] In addition, because only mild adverse events have been previously associated with pemetrexed, its use in maintenance therapy is promising. In the JMEN trial, switch maintenance therapy with pemetrexed was associated with prolonged OS and progression-free survival (PFS) in patients with nonsquamous NSCLC without disease progression after platinum doublet therapy.[7] Platinum and pemetrexed followed by pemetrexed continuation maintenance therapy has also become a standard treatment in advanced nonsquamous NSCLC and was reported to significantly prolong OS and PFS in patients in the PARAMOUNT trial.[8] Subsequently, platinum combined with pemetrexed and pemetrexed maintenance has become the standard treatment for patients with advanced nonsquamous NSCLC.

Several studies have compared maintenance therapies using bevacizumab or pemetrexed or a combination of both, and the combination of bevacizumab and pemetrexed has been shown to prolong PFS compared with single agent therapy, although did not improve the OS, and patients have been reported to suffer more adverse effects from combined maintenance therapy. Therefore, maintenance using a single agent, or combination therapy, is reasonable for patients with nonsquamous NSCLC.[9]

Bevacizumab, the first antiangiogenetic monoclonal antibody, combined with platinum-base double agent chemotherapy, has previously been reported to improve PFS in advanced nonsquamous NSCLC patients, and improve overall survival (OS) when combined with carboplatin and paclitaxel in Caucasian and in Chinese patients.[10, 11] The advantage of bevacizumab not only comes from its combination with platinum-based double agent chemotherapy, but also in maintenance therapy. Bevacizumab has also been reported to cause the most safety problems, such as more serious hypertension, proteinuria and decrease in WBCs, while increasing the ORR and improving patient survival. The BEYOND study includes Chinese patients, and reported that the ORR, stable disease rate and progressive disease rate was 54%, 40% and 2% in patients receiving bevacizumab plus carboplatin/paclitaxel, and 26%, 62% and 8% in patients receiving a placebo plus carboplatin/paclitaxel. We hypothesis that some patients with stable disease and progressive disease in chemotherapy group may become partial response and stable disease separately when adding bevacizumab in the regimen, in other word, the improvement of response rate in bevacizumab group come from the stable disease and progressive disease in chemotherapy group.

As a major part of nonsquamous NSCLC, pulmonary adenocarcinoma is the most common type seen in clinical practice. Not only from clinical studies, but also our real-world experience, bevacizumab has been shown to improve response and survival in patients, but also cause more adverse effects, such as hypertension, bleeding and proteinuria, etc.

For the above reasons, we launched this study in patients with advanced pulmonary adenocarcinoma with stable disease after two cycles of platinum-based double agent chemotherapy (registered as Clinical Trial NCT03240549).

Methods/design

Objectives

The main purpose of this prospective cohort study is to confirm our hypothesis that adding bevacizumab improves the response rate compared with continuing original treatment in advanced stage pulmonary adenocarcinoma in patients with stable disease after two cycles of platinum-based double agent chemotherapy. The primary endpoint is the objective response rate (ORR). The second endpoints include PFS, safety of bevacizumab and quality of life in each group.

Eligibility criteria

Patients with advanced lung adenocarcinoma age 18 to 75 years old, confirmed histologically or cytologically, but not by sputum cytology, and with stable disease according to RECIST 1.1 after two cycles of platinum plus pemetrexed or paclitaxel chemotherapy will be included in this study. Patients with epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase gene fusion may also be included if treatment with tyrosine kinase inhibitors (TKIs) has been unsuccessful. The patients should have an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematological, hepatic or renal function. There should not be any contraindication to the administration of bevacizumab or have been any previous dose adjustment due to adverse effects of chemotherapy. All patients must provide their written informed consent to be included in the study.

Exclusion criteria

Patients diagnosed with mixed non-small cell and small cell carcinoma, large cell carcinoma, adenosquamous

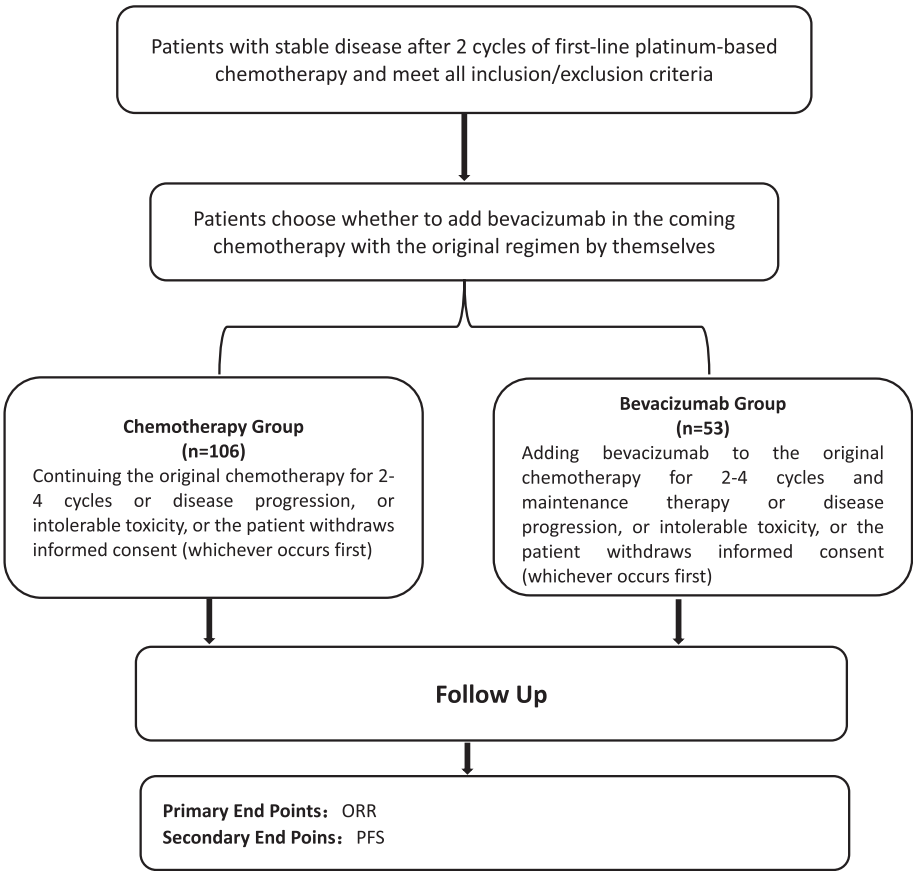

Figure 1 Reasearch process.

carcinoma or with a history of hemoptysis (a single hemoptysis of more than 2 mL blood) within three months before selection, or where imaging has confirmed signs of tumor invasion into the large blood vessels will not be permitted to enter the trial.

The exclusion criteria also includes: (i) symptomatic central nervous system metastasis or intratumoral hemorrhage; (ii) chest radiotherapy within 28 days prior to enrollment into the study; (iii) current or recent (within the first 10 days of receiving the first dose of bevacizumab) use of full dose oral or parenteral anticoagulant or thrombolytic therapy; (iv) medical history or examination results which indicate there is a hereditary bleeding tendency or coagulopathy which may increase the risk of bleeding; (v) uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), or previous hypertensive crisis or hypertensive encephalopathy patients; (vi) significant vascular disease (including but not limited to aortic aneurysm or proximal arterial thrombosis requiring surgical repair) within six months prior to enrollment and non-curative wounds; (vii) active peptic ulcers or fractures; and (viii) hypersensitivity to bevacizumab or any of its excipients and any chemotherapeutic ingredients.

Study design and treatment plan

Patients with advanced pulmonary adenocarcinoma who have received platinum-based therapy plus pemetrexed or paclitaxel chemotherapy in standard dose, who have a stable disease according to RECIST 1.1 after two cycles of treatment without dose decrease are suitable for this study. Patients will be able to continue their original platinum-based double agent chemotherapy or they can choose to add bevacizumab to their regimen following their written informed consent.

The patients who continue with their original platinum-based chemotherapy will receive the former treatment without any dose adjustment. The other patients in the bevacizumab group will receive bevacizumab 15 mg/kg together with their original chemotherapy regimen and dosage. The first platinum we preferred is carboplatin at a dose of AUC 5, pemetrexed at a dose of 500 mg/m^2 and paclitaxel dose of 175 mg/m^2.

Patients who experience grade 3 or more severe adverse effects and delay in treatment according to adverse effects will be removed from the study.

The ORR will be evaluated every two cycles, and the patients who did not progress after another two or four cycles can select maintenance therapy or stop treatment by themselves (Fig 1).

Expected results

The improvement in ORR was 28% and 20% in the BEYOND[11] and ECOG4599 studies[10] when bevacizumab was added to chemotherapy separately, and patients with stable disease who continued with their original chemotherapy had a 15% ORR after two cycles of platinum-based chemotherapy.[12] We therefore assume that ORR in the group in which bevacizumab was added showed an improvement of 20% compared with 15% in the other group where patients continued with the original chemotherapy. At least 53 and 106 patients would be included in the trial separately based on this hypothesis at a ratio of 1:2 and power of test is 0.8 in two- sided 0.05 test level.

Analytical method

The ORR is the complete response plus partial response according to RECIST 1.1 in the combination treatment, and the Chi-square test is used to evaluate the difference of ORR between the two groups. The PFS is defined as the time from treatment after informed consent to the day of disease progression or death. The Kaplan-Meier method will be used to estimate the median duration and 95% confidence interval for each group of PFS. Stratified and unstratified Cox regression analysis and log rank sum test will be used to estimate the hazard ratio (HR).

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Disclosure

No authors report any conflict of interest.

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