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REVIEW

Bevacizumab in combination with anticancer drugs for previously treated advanced non-small cell lung cancer

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Abstract Non-small cell lung cancer (NSCLC) accounts for about 85 % of all lung cancer cases. Patients with NSCLC often have an advanced disease at the time of diagnosis, with a 1-year survival rate about 10–15 % under the best support treatment. As therapeutic methods for lung cancer developed rapidly in recent years, the prognosis of stage IIIB or IV NSCLC also improve to a large extend. Bevacizumab is a monoclonal antibody against VEGFR which inhibits abnormal vascular growth in malignant tumors. In October 2006, bevacizumab was approved by the U.S. Food and Drug Administration (FDA) for first-line use in advanced NSCLC. For patients with advanced NSCLC who failed in previously platinum-based chemotherapy, bevacizumab also showed enhancing efficacy to antitumor drugs recommended by the latest NCCN guideline. This review intends to present the recent progress and prospects of bevacizumab in second- or third-line treatment for patients with refractory NSCLC.

Keywords Non-small cell lung cancer (NSCLC) · Bevacizumab · Platinum-based chemotherapy

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Abbreviation

NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
FDA	The U.S. Food and Drug Administration
ECOG	Eastern Cooperative Oncology Group
SD	Stable disease
PR	Partial remission
CNS	Central nervous system
RECIST	Response Evaluation Criteria in Solid Tumors
PFS	Progression-free survival
OS	Overall survival
EGFR	Epidermal growth factor receptor
VEGFR	Vascular epidermal growth factor receptor

Background of NSCLC

Each year, approximately 2.2 million new cases of lung cancer are diagnosed worldwide and 1.7 million cancer-related deaths occurred among such patients [1]. Lung cancer is currently classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter of which accounts for approximately 85 % of all cases [2, 3]. Patients with NSCLC often have an advanced disease at the time of diagnosis, with a 1-year survival rate about 10–15 % under the best support treatment [4].

Bevacizumab in first-line setting

Although platinum-based chemotherapy is the standard treatment for advanced NSCLC, patients with this disease only have a median survival time of 8 to 10 months [5–9]. As therapeutic methods for lung cancer developed rapidly in recent years, the prognosis of NSCLC also improve to a large

extend. As known to us, angiogenesis is necessary for cancer cells to proliferate and metastasize and that the vascular endothelial growth factor (VEGF) plays an important role in promoting tumor angiogenesis [10–14]. Previous studies indicate that VEGF, which is mediated by vascular endothelial growth factor receptor (VEGFR), is over expressed in a variety of malignant tumors [15–17]. Bevacizumab is a monoclonal antibody against VEGFR, and hence exert antitumor effect by inhibiting abnormal vascular growth in malignant tumors [18–20]. In a phase III study, bevacizumab-enhanced median progression-free survival (PFS) and median overall survival (OS) to approximately 6 and 12 months, respectively, with controllable toxicities, when combined to chemotherapy for nonsquamous stage IIIB and IV NSCLC patients(E4599) [21]. Based on this encouraging result, the U.S. Food and Drug Administration (FDA) granted approval for bevacizumab for first-line use in advanced NSCLC in October 2006 [22]. In order to determine the best dose used in the clinic, another phase III trial (AVAiL) was conducted to evaluate the effect of bevacizumab (7.5 and 15 mg/kg every 3 weeks) in combination with gemcitabin and cisplatin in the first-line management of advanced NSCLC [23]. Final analysis of AVAiL confirms the efficacy of bevacizumab when combined with this chemotherapy regimen.

Between August 2006 and June 2008, a phase 4 study named SAiL (Safety of Avastin in Lung) was undertaken to further evaluate the safety and efficacy of first-line bevacizumab combined with standard platinum-based chemotherapy in patients with advanced or recurrent non-squamous NSCLC [24]. Two thousand two hundred twelve patients were assessed in the study and the result was optimistic. The efficacy of bevacizumab was even better than that reported in the previous two large phase III study [21, 23], with a median PFS of 7.8 months and a median OS of 14.6 months. Since the primary endpoint of this study is safety, the investigators recorded all the adverse events probably associated with bevacizumab and found that the episode of grade 3 or higher toxicities was relatively low. The most common grade 3 or higher adverse events were thromboembolism (8 %), hypertension (6 %), proteinuria (3 %), bleeding (4 %), and pulmonary hemorrhage (1 %). The results of the SAiL study further demonstrated the safety and efficacy of bevacizumab plus platinum-based chemotherapy regimens in the first-line treatment of patients with advanced or recurrent non-squamous NSCLC.

Bevacizumab for previously treated NSCLC

Worldwide, bevacizumab is administrated generally in patients with advanced nonsquamous NSCLC who were chemotherapy naïve. If patients failed in previously first-line therapy of erlotinib, platinum-based chemotherapy combined with bevacizumab may be still effective as second-line treatment for patients with lung adenocarcinoma who have a performance status ≤2. Currently, three single antitumor agents, erlotinib [25], docetaxel [26, 27], and pemetrexed [28], were recommended by the NCCN guideline for those with advanced NSCLC who failed in the front-line therapy. Hence, we wonder whether bevacizumab has an enhancing therapeutic effect to NSCLC when used with any of the above three antitumor agents.

In recent years, several studies reported that the combination of bevacizumab plus erlotinib showed efficacy to advanced NSCLC when used in previously treated NSCLC [29, 30]. As known to us, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKIs), erlotinib, and gefitinib demonstrated superior efficacy against advanced NSCLC as single treatment [31, 32]. However, when combined to chemotherapy, neither drug showed further benefit to patients with advanced NSCLC [33–35]. In cells, EGFR and VEGFR share common downstream signaling pathways, thus may exert increased effects both directly and indirectly on tumor cells. It is supposed that the combination of drugs that target these two molecules may produce additional clinical benefit to patients with advanced NSCLC.

A phase I/II study was thus performed in two medical centers in the USA, aiming to evaluate the safety and efficacy of bevacizumab (15 mg/kg, every 3 weeks) plus erlotinib (150 mg/day) to treat patients with stage IIIB or IV, recurrent, nonsquamous NSCLC [29]. In total, forty patients, with a median age of 59 years, were enrolled on this study, of whom 37 (≥90 %) had a Karnofsky performance score ≥80 at screening and 9 (22.5 %) never smoked. Of all the patients randomized in the study, 32 (80 %) had stage IV disease and 30 (75 %) had adenocarcinoma. All patients failed at least one prior platinum-based regimen and 22 (55 %) of whom received two or more prior systemic chemotherapy regimens for NSCLC. In the study, eight patients (20.0 %) obtained partial responses and 26 (65.0 %) had stable disease. The median OS was 12.6 months in the phase II section, with a median PFS 6.2 months. The most commonly reported adverse events were mild to moderate, including rash (85 %), diarrhea (65 %), infection (29 %), hematuria (32 %), proteinuria (9 %), and epistaxis (6 %). Grade 3/4 adverse events in the phase II section included hypertension (n=2), rash (n=1), pruritus (n=1), and pneumonia (n=3), as compared with no treatment-related grade 3 or higher adverse events in the phase I section. No severe thromboembolism or hemoptysis was reported in the study. These results indicated that the combination of bevacizumab and erlotinib was safe and effective for previously treated advanced NSCLC.

The efficacy of administration with the anti-VEGF monoclonal antibody bevacizumab and the EGFR small-molecule tyrosine kinase inhibitor erlotinib was further confirmed in a large, multicenter, randomized phase II trial conducted

between October 2004 and November 2005 [30]. The aim of this study was to evaluate the effect of bevacizumab (15 mg/kg, every three weeks) combined with erlotinib (150 mg/day) or chemotherapy (500 mg/m^2 pemetrexed and 75 mg/m^2 docetaxel) and that of chemotherapy alone in previously treated NSCLC. Patients who had a progression disease after one platinum-based chemotherapy regimen for unresectable locally advanced or metastatic nonsquamous NSCLC were qualified for this study. Key exclusion criteria included any antitumor therapy within 4 weeks before random assignment, history of hemoptysis or presence of cavitation, history of central nervous system (CNS) metastases, full-dose anticoagulant use, or presence of a central lesion. Totally, one hundred and twenty patients were enrolled, and all the patients are randomly assigned and treated. In detail, 39 (32.5 %) patients received bevacizumab plus erlotinib, 40 (33.3 %) patients received chemotherapy plus bevacizumab, and 41 (34.2 %) patients received chemotherapy (docetaxel or pemetrexed) plus placebo. Treatment continued until disease progression or through 52 weeks. Final results showed that the therapy of bevacizumab in combination of erlotinib or chemotherapy produced response rates of 51.3 and 52.5 %, respectively, as compared with a response rate of 39 % in the arm of chemotherapy alone. The median OS were 13.7, 12.6, and 8.6 months for bevacizumab plus erlotinib, bevacizumab plus chemotherapy and chemotherapy alone arms, whereas the median PFS were 4.4, 4.8, and 3.0 months, respectively. No clinically significant differences were found between bevacizumab plus erlotinib arm and bevacizumab plus chemotherapy arm. In the study, hematologic adverse events occurred more frequently in chemotherapy-treated patients, whereas the incidence of fatal pulmonary hemorrhage and thrombosis were significantly greater in bevacizumab-treated patients, which was consistent with that in previous bevacizumab studies. Overall, the toxicity profile of the bevacizumab-erlotinib regimen was favorable compared with the other two combinations. Based on the above results, a randomized phase III trial was ongoing to further comparing erlotinib plus bevacizumab with erlotinib alone in the second-line setting for previously treated NSCLC.

In chemotherapy-containing arms of the above phase II trial, 35 patients received pemetrexed and 46 patients received docetaxel. Confirmed in previous studies, pemetrexed was more effective than other single chemotherapeutic agents for nonsquamous NSCLC [36, 37]. However, OS in patients who received pemetrexed alone was not as long as previously observed, which was referred in this study. One probable reason is that the number of patients enrolled was too small, another is that the follow-up time was not enough. Later, a retrospective study compared the combination of bevacizumab plus pemetrexed with pemetrexed alone in the treatment of NSCLC patients who had received at least one prior chemotherapy regimen [38]. There were 25 patients treated in the study, 9 with bevacizumab (15 mg/kg every 3 weeks) combined with pemetrexed (500 mg/m^2 every 3 weeks), and 16 with pemetrexed alone. Dexamethasone, folic acid, and vitamin B12 were administered routinely, and treatment continued until patients having a progressed disease. In the study, no grade 3 through 5 hemorrhagic toxicities was reported. Grade 3 neutropenia, anemia, and thrombocytopenia were observed in the combination group and grade 3/4 neutropenia was reported in pemetrexed alone group. Final analysis showed that there were no differences between the two study groups in median OS (10.92 versus 8.64 months, respectively), median TTP (1.56 versus 2.06 months), or objective response (55.5 % versus 50 %). The 6-month survival rate was 66.7 % for the bevacizumab-pemetrexed group and 56.3 % for the pemetrexed alone group. This study showed that the combination of bevacizumab and pemetrexed was safe and effective to patients with refractory NSCLC. However, whether bevacizumab own the ability to enhance the efficacy of pemetrexed remain unknown.

To solve this problem, a phase II study was conducted from May 2006 to February 2007 [39]. In the study, the efficacy and toxicity of bevacizumab combined with pemetrexed was evaluated as second-line therapy for patients with advanced NSCLC. Forty-eight patients were enrolled in seven medical centers in the USA and all of them received bevacizumab 15 mg/kg with pemetrexed 500 mg/m^2 every 3 weeks for a median of four cycles. Toxicities of this combination were tolerable. Grade 3 or higher toxicities were seen in 42 patients (88 %), the most common of which were neutropenia (19 %), leukopenia (17 %), lymphopenia (13 %), fatigue (13 %), dyspnea (10 %), and thrombosis (10 %). The disease control rate was 50 % among all 48 patients, of whom five achieved confirmed PR and 19 obtained SD. The median OS was 8.6 months and median PFS was 4.1 months, the latter of which was improved in this study, as compared with the PFS of 2.9 months reported for several single chemotherapeutic drugs used in the clinic as second-line treatment for stage IIIB or IV NSCLC. This study also found that the regimen of bevacizumab plus pemetrexed may be particularly effective for patients with advanced NSCLC who own specific genotypes of SLC19A1, GGH, and FPGS. Hence, the authors concluded that bevacizumab may have potential ability to increase the efficacy of pemetrexed in these genotypes.

To date, combination chemotherapy is still the standard treatment for first-line therapy of advanced NSCLC. Although the combination of bevacizumab plus single antitumor agents (erlotinib and pemetrexed) showed promising effects to previously treated NSCLC, the efficacy of adding bevacizumab to platinum-based regimen in second-line and beyond settings remain unknown. Therefore, a phase II study was conducted between January 2005 and October 2006 to evaluate bevacizumab (15 mg/kg), oxaliplatin (120 mg/m^2), and pemetrexed (500 mg/m^2) administered every 3 weeks for

patients with refractory nonsquamous NSCLC [40]. A total of thirty-six patients were enrolled on this study, including those with brain metastases. Treatment sustained for 6 cycles or until disease progression or unacceptable toxicity. A median of 5.5 cycles were administered, which yielded a response rate of 27 % and a clinical beneficial rate of 71 % among 34 evaluable patients. Importantly, the median PFS was 5.8 months and median OS was 12.5 months. For patients with advanced NSCLC who failed in previously standard therapy, these survival data was encouraging. In addition, toxicities of this combination were generally tolerable. The most common grade 3 or higher adverse event was hypertension, which occurred in six patients. Although nine patients with brain metastases were enrolled, no events of brain hemorrhage were observed in the study. Actually, this regimen produced promising efficacy with manageable toxicity for patients with previously treated advanced NSCLC. Based on these results, the authors recommended that a randomized trial should be performed to compare the effect of bevacizumab, oxaliplatin, and pemetrexed with bevacizumab and pemetrexed.

Summary and prospects for bevacizumab

Since NSCLC remains one of the most lethal cancers in the world, researchers have been working vigorously in the hope of finding innovative ways of tackling this disease. Bevacizumab is a monoclonal antibody against VEGF, which is producing encouraging antitumor effect in the clinic. Nowadays, bevacizumab are approved to be administered only in chemotherapy naïve nonsquamous NSCLC. For patients who failed from standard platinum-based chemotherapy, the best therapeutic strategy is prescription of single agents, such as erlotinib and pemetrexed. However, several studies have showed that bevacizumab combined with antitumor drugs may obtain better efficacy in selected patients with previously treated NSCLC. Three important selective factors are performance status, tumor histology, and molecular characteristics. Patient age and cardiovascular status should also be considered to reduce unwanted adverse events. Finally, more clinical trials are needed to further elaborate the relationship between bevacizumab and refractory NSCLC.

Conflicts of interest None

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