Apatinib is effective as third-line and more treatment of advanced metastatic non-small-cell lung cancer
A retrospective analysis in a real-world setting

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Abstract
No standard methods are recommended for patients with advanced metastatic non-small-cell lung cancer (NSCLC) experiencing progression after 2 or more lines treatment now. The aim of this retrospective study was to assess the efficacy and safety of apatinib in metastatic NSCLC patients after second-line or more treatments failure in a real-world setting.

A total of 52 advanced NSCLC patients who experienced progression after second-line and more treatments and received apatinib from March 2016 to February 2018 were retrospectively reviewed. Patients were treated with oral apatinib 500 mg QD (take the medicine once a day), every 4 weeks for a cycle. Responding and stable patients continued the treatment until progression or intolerable toxicity. The overall survival (OS), progression-free survival (PFS), objective remission rate (ORR) and disease control rate (DCR), and side effects of the drug were collected and reviewed.

The ORR and the DCR were 6.9% and 67.4%. The median PFS and median OS of all patients were 3.8 months and 5.8 months, respectively. The Eastern Cooperative Oncology Group score was the independent influencing factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens (PFS: hazard ratio [HR] = 4.446, 95% confidence interval [CI]: 1.185–16.678, P = .027 and OS: HR =8.149, 95% CI: 1.173–56.596, P = .034). The most common adverse events apatinib-related included hypertension (19.2%), hand-foot syndrome (11.5%), and mucous membrane reaction (17.3%). And treatment-related grade 3/4 toxicities were low.

Apatinib showed favorable efficacy and safety and could be a treatment option in patients with advanced NSCLC experiencing progression after second-line and more treatment.

Abbreviations: CR = complete response, DCR = disease control rate, ECOG = Eastern Cooperative Oncology Group, ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = epithelial growth factor receptor, NSCLC = non-small-cell lung cancer, ORR = objective remission rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, REGIST = response evaluation criteria in solid tumor, SD = stable disease, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

Keywords: anti-angiogenic drugs, apatinib, non-small cell lung cancer, targeted therapies, vascular endothelial growth factor receptor

1. Introduction
Lung cancer is one of the most common malignancies and the leading cause of cancer-related death in the world and China. Non-small cell lung cancer (NSCLC) has the highest incidence, accounting for over 80% of lung cancer patients. As the early symptoms are not obvious, the vast majority of lung cancer patients have been diagnosed at the advanced stages.\textsuperscript{[1]} Despite the significant progress with the targeted and immunotherapeutic agents in the treatment of advanced NSCLC over the last decade, there is no standard treatment for patients with advanced metastatic NSCLC experiencing progression after 2 or more lines of standard treatment. Currently, Clinical trials or palliative care are generally recommended by the guidelines. For these patients with acceptable Eastern Cooperative Oncology Group (ECOG) scores, whether antiangiogenic drugs with definite curative effect and small side effect could be an option is widespread concerned.

Vascular endothelial growth factor (VEGF) family proteins are the most important cytokines that induce tumor angiogenesis.\textsuperscript{[2]} The VEGF family consist of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor. VEGF-A can increase vascular permeability and promote
angiogenesis. VEGF-B forms a dimer with VEGF-A to exert its effect. The transmembrane receptors required for VEGF family signaling include Flt-1 (VEGFR-1), KDR (VEGFR-2), Flt-4 (VEGFR-3), Neuropilin-1, and Neuropilin-2. Transmembrane receptors have an intrinsic tyrosine kinase activity. VEGF stimulates downstream signal transduction by binding to tyrosine kinases of transmembrane receptors and promotes proliferation, mitosis, differentiation, and migration of endothelial cells to form new vascular cavities.

As a new target in the treatment of cancer, antiangiogenic drugs have been actively investigated in tumors. Bevacizumab, a recombinant humanized monoclonal antibody against VEGF, is the first antiangiogenic drug approved by the Food and Drug Administration, which is now widely used in the treatment for cancer. Clinical evidence from ECOG 4599 and AVAIL had laid the foundation for bevacizumab combined with standard chemotherapy alone, patients with advanced NSCLC had higher response rates and prolonged time to progression when treated with bevacizumab combined with standard chemotherapy.

Apatinib (HengRui Pharmaceutical Co, Ltd, Lianyungang, People's Republic of China), is a novel small molecule tyrosine kinase inhibitor which was approved in China in 2014. Apatinib binds to the VEGFR-2 ATP binding site and selectively inhibits the phosphorylation of VEGFR-2 and tumor angiogenesis. Based on a promising phase III study in Chinese gastric cancer patients, apatinib had been admitted as a standard third line treatment for advanced gastric cancer in China. Apatinib has also been used in some small clinical practice or case report and has some potential efficacy as a salvage treatment for other advanced metastatic tumor such as breast cancer, esophageal cancer. However, there is no standard on the selection of case and treatment timing for patients with apatinib in solid tumor.

In this study, we retrospectively evaluated the efficacy and the safety profiles of apatinib in advanced NSCLC patients who had failed with second-line or more treatments in our medical center in a real-world treatment patterns. Clinicopathologic factors associated with prognosis were also concerned.

2. Material and methods

2.1. Patient selection

All the patients were treated in Chongqing University Cancer Hospital between March 2016 and February 2018. Fifty-two advanced NSCLC patients who experienced progression after second-line and more treatments and received apatinib were included. The study protocol was approved by the Ethics Committee of Chongqing University Cancer Hospital. All participants provided informed consent before treatment.

Data were collected from the medical records and radiographic imaging records included gender, age, smoking history, histology, endothelial growth factor receptor (EGFR) mutation type, ECOG performance status, previous treatment, response, adverse events, and survival data. Inclusion criteria included: pathologically diagnosed or recurrent stage IV NSCLC; ECOG 0 to 2; at least 1 radiologically measurable lesion did not receiving local treatments such as radiotherapy and freezing; progression after previously second-line and above standard treatments, including molecular targeted therapy according to gene mutations and/or platinum-based chemotherapy and/or radiotherapy; no other active antitumor treatments were offered during the period of apatinib treatment; no history of severe heart disease, and liver and kidney function and bone marrow hematopoiesis are normal. The main exclusion criterion was patients with uncontrolled blood pressure with medication (>140/90 mm Hg) and with those with bleeding tendency and receiving thrombolytics or anticoagulants.

2.2. Treatment regimen

Patients were treated with oral apatinib at a daily dose of 500 mg, every 4 weeks for 1 treatment cycle. Dose reduction (250 mg QD) was allowed for drug-related toxicity. Re-evaluating computed tomography (CT) scans will be carried out after 2 cycles of treatment. Responding and stable patients continued the treatment until progression or unacceptable toxicity. Follow-up time was until the death of the patient or the end of the study.

2.3. Responses and toxicity assessments

The size of measurable lesions was determined by CT scan every 2 cycles. The tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1 criteria. Tumor efficacy was evaluated included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective remission rate (ORR) was defined as the percentage of CR and PR. The disease control rate (DCR) was defined as the percentage of CR and PR and SD. In addition, toxicities were assessed by the National Cancer Institute Common Toxicity Criteria version 4.0.

2.4. Follow-ups

Progression-free survival (PFS) was defined as the period between the first date of apatinib treatment and the date of progression. Overall survival (OS) was defined as the period from the first date of apatinib treatment to death or the study ending. Follow-ups were conducted up to February 28, 2018. And the median follow-up period was 11.3 month (2.9–21 m).

2.5. Statistical analysis

Data analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, IL). The Kaplan–Meier method was performed to survival analysis for PFS and OS. The multivariate Cox regression model was used to estimate the treatment hazard ratios. Differences with a 2-sided P-value of <.05 were considered statistically significant.

3. Results

3.1. Patients characteristics

A total of 52 patients retrospectively were collected. The patient’s general information included gender, age, and pathological types, smoking status, EGFR mutations, ECOG scores, and prior treatment. Among them, 44 were male and 8 were female with a median age of 61 years (with the range of 32–77 years). According to their gene sensitizing gene mutations, all of them had received targeted treatment and/or platinum-based chemotherapy and/or radiotherapy before. Detection of EGFR gene by tissue had shown 6 of 8 patients
were deletion of exon 19, while 1 was L858R in exon 21 and 1 was mutations in exon 20. And 43 patients had a PS of ECOG 0 or 1 and 9 patients had a PS of 2. The patients’ characteristics are summarized in Table 1.

### 3.2. Survival and response

Nine of the 52 patients were not eligible for evaluation of the efficacy. Among these 9 patients, 7 patients could not follow-up. Another 2 patients stopped treatment after 2 weeks due to the sudden hemoptysis. A total of 43 patients were evaluated for efficacy. A total of 3 patients (6.9%) achieved PRs with an ORR of 6.9%. Twenty-six patients (60.5%) archived a SD status and 14 patients (32.6%) archived PD with a DCR of 67.4%. The median progression-free survival (PFS) and median OS of all patients treated with apatinib as third-line or more were 3.8 months and 5.8 months, respectively (Figs. 1 and 2).

Cox method was used for the univariate analysis of 43 patients with advanced NSCLC experiencing progression after 2 or more lines of treatment. Cox univariate analysis showed that ECOG score affected the PFS and OS of apatini treated advanced NSCLC patients who failed above second line. Patients with ECOG 0–1 scores had prolonged PFS compared with ECOG 2 patients (3.9 months vs 2.1 months, respectively, \(P = .029\)). And patients with ECPG 01 scores also had longer OS than that of ECOG 2 (6.4 months vs 4.1 months, \(P = .046\)). The gender, age, smoking status, pathology type and EGFR status of the patients were not the predictors of PFS and OS (Table 2).

The multivariate analysis also showed that the ECOG score was the independent factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens (PFS: hazard ratio [HR] = 4.446, 95% confidence interval [CI]: 1.185–16.678, \(P = .027\); OS: HR = 8.149, 95% CI: 1.173–56.596, \(P = .034\)). The results are listed in Table 3.

### 3.3. Adverse events

The most common treatment-related adverse events of all levels were as follows: hypertension 19.2% (10/52), hand-foot syndrome 11.5% (6/52), gastrointestinal reactions 13.5% (7/52), mucous membrane reaction 3.8% (2/52), palpitation 5.8% (3/52), hemoptysis 3.8% (2/52), proteinuria 1.9% (1/52). The symptoms related to treatment-related adverse events of grade 3 accounted for 13.5%, including hypertension (n = 2), of which 1 case considered mild cerebral hemorrhage, palpitations (n = 2), hemoptysis (n = 2), thrombocytopenia (n = 1). The symptoms related to treatment-related adverse events of grade 3 were quickly reduced and recovered after a dose reduction and symptomatic treatment in time. Dose reduce were not needed for these grade I-II adverse events and the symptoms could be controlled well. There were no drug-related serious adverse events.

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**Table 1**

| Characteristic          | Number of patients | Percentage (%) |
|-------------------------|--------------------|----------------|
| Gender                  |                    |                |
| Male                    | 44                 | 84.6           |
| Female                  | 8                  | 15.4           |
| Age                     |                    |                |
| <65 yr                  | 33                 | 63.5           |
| ≥65 yr                  | 19                 | 36.5           |
| Histology               |                    |                |
| Adenocarcinoma          | 32                 | 61.5           |
| Squamous cell carcinoma | 20                 | 38.5           |
| Smoking history         |                    |                |
| Yes                     | 41                 | 78.8           |
| No                      | 11                 | 21.2           |
| EGFR mutation           |                    |                |
| Mutation                | 8                  | 15.4           |
| Wide type               | 26                 | 50             |
| Unknown                 | 18                 | 34.6           |
| ECOG PS                 |                    |                |
| 0–1                     | 43                 | 82.7           |
| 2                       | 9                  | 17.3           |
| Previous treatment      |                    |                |
| Targeted therapy + chemotherapy | 5 | 9.6 |
| targeted therapy + chemotherapy + radiotherapy | 5 | 9.6 |
| Chemotherapy            | 17                 | 32.7           |
| Chemotherapy + radiotherapy | 25 | 48.1 |

**Note:**

ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth factor receptor.
reactions occurred in this study. The side effects are listed in Table 4.

4. Discussion

In 1971, Professor Folkman proposed the theory of “starving tumors.” The theory was that tumors need new blood vessels to provide rich nutrition and nutrients. By blocking the blood supply of tumors, tumor lesions could be no more than 2 to 3 mm.[18] VEGF is a key mediator with neovascularization and the expression of VEGF in tumor is closely related to the early recurrence, metastasis and the prognosis of the tumor.

The family of VEGF and their receptors (vascular endothelial growth factor receptor [VEGFR]) were overexpressed on the surface of malignant tumors.[19] VEGFR-2 is the most important VEGFR and it is mainly expressed on the surface of vascular endothelial cells and bone marrow-derived endothelial cells.[20] Increased VEGFR-2 gene copy number was found in NSCLC tumor tissue.[21,13] The overexpression of VEGFs and VEGFRs plays an important role in the survival of patients with NSCLC.[13]

Although a few angiogenesis inhibitors such as bevacizumab combined with chemotherapy have shown improved OS or PFS in patients with lung, breast, renal, hepatic, and colon cancers,
agents in angiogenesis alone had shown limited clinical value in metastatic NSCLC cancer.

Apatinib, one of the latest oral small-molecule angiogenesis inhibitors, selectively inhibits VEGFR-2, which may inhibit VEGF-stimulated endothelial cell migration and proliferation and decrease tumor growth and metastasis.[10,13] Li[12] had reported a randomized, placebo-controlled phase III study of Apatinib in Chinese gastric cancer patients. Two hundred seventy-three advanced gastric cancer patients after second-line failure were randomly assigned to receive 850mg of apatinib and placebo in 2:1 ratio. Patients with apatinib had a significantly prolong the median OS compared with those treated with placebo (6.5 months vs 4.7 months, \(P=.0149\)). The study in breast cancer patients who used apatinib as the salvage treatment also had similar prolonged PFS and OS (3.3 months for PFS and 10.7 months for OS).[13]

For advanced NSCLC patients who have failed after second-line or more radiochemotherapy or targeted treatment, no definitive chemotherapeutic regimen has been recommended now. New treatment strategy is urgently needed especially for those who had a better performance status (PS). Song[22] analyzed the efficacy of apatinib as a salvage treatment in 42 advanced NSCLC patients. Apatinib was approved effective in patients who were unresponsive to standard pretreatment before. In our study, the objective response rate and he DCR of apatinib were significantly higher and longer consistent with the previous study in the Chinese population. Our study, the objective response rate and the DCR of apatinib were significantly higher and longer than that used placebo (6.5 months vs 4.7 months, \(P=.0149\)). The study in breast cancer patients who used apatinib as the salvage treatment also had similar prolonged PFS and OS (3.3 months for PFS and 10.7 months for OS).[13]

In our study, Cox univariate analysis showed that ECOGs score affected the PFS and OS of apatinib treated advanced NSCLC above second lines. The gender, age, smoking status, pathology type and EGFR status of the patients were not the predictors of PFS and OS. In order to eliminate confounding factors, this study continued to use the cox proportional regression risk model for multivariate analysis. The multivariate analysis also showed that the ECOG score was the independent factor of PFS and OS for the advanced NSCLC patients who were treated with apatinib after second-line and above standard regimens. Apatinib maybe a treatment choice for these NSCLC patients who had a better PS. For various reasons, half of our patients did not undergo mutation gene detection during their course of disease. The multivariate analysis showed that previous treatments and EGFR mutation weren’t the independent factor of PFS and OS for the patients.

The adverse events of apatinib especially III-IV grade side effects in different studies might be caused by the different dose and different cancer. The recommended dose for apatinib is 850 mg. While many trials had found the daily apatinib dose of 500 mg could have the similar efficacy as those of high dose while decrease the grade 3/4 toxicities significantly.[13,11,13] One of a small retrospective study[23] had reported a daily dose of 250mg of apatinib was safe and effective in the treatment of NSCLC. In our center, a common recommended dose of 500 mg was used for more lines treated solid cancer patients considering the efficacy. And the majority of our patients were also willing to accept this dose for cost-effectiveness reasons too. Previous studies have found that the most common adverse events of apatinib were hypertension, hand-foot skin reactions, and proteinuria.[22–25] although some case report showed gastrointestinal hemorrhage and perforation during apatinib treatment.[26] Most of studies had supported that the adverse events of apatinib were dose-dependent and grade 3 to 4 side effects had found rare in low dosage.[22–23] In our study, apatinib-related grade 3 toxicities occurred in 13.5% patients, which were lower than that in gastric carcinoma patients.[12] The symptoms of III-IV grade side effects hypertension could be well controlled by drug suspension or dose reduction and symptomatic treatment. In our study, the common hematologic toxicities related to apatinib were mild. The toxicities of apatinib are similar to or better than those of other antiangiogenic drugs such as Bevacizumab[9,27] or rh-endostatin.[89] It seems that apatinib was safe in comparison with other antiangiogenic agents, especially lower than that in chemotherapeutics.[29–31] This means apatinib maybe a promising alternative therapy for patients who had undergone more lines treatments.

In summary, our current real-life setting study data provides a valuable real-life evidence regarding treatments received apatinib in advanced NSCLC patients after more lines treatment. The major limitations of this study were retrospective nature and a small sample size. Compared with prospective studies, there may be potential biases in the selection of possible cases and may affect the conclusions in retrospective study. Even Statistical analysis was used to reduce unmeasured confounding factors, the small number of patients still limited in its ability to provide better conclusion. More prospective study with a chemotheraphy or palliative treatment control group will give us a more credible conclusion. There are many questions should be answer in apatinib treatment in NSCLC. What is the appropriate cases for apatinib treatment and when is the best time to use apatinib in advanced NSCLC patients? Could the combination of apatinib and chemotherapy improve the benefit in NSCLC patients? To answer these questions, more clinical studies will needed; and furthermore, these questions can be offered for clinical treatment. In addition, the dose of 500 mg apatinib adopted in this study was not widely recommended. Hence, the most suitable dosage is needed be verified by further prospective large-scale studies. However, without prospective clinical studies in the literature, since our patients chose apatinib treatment randomly, our conclusion may be deemed as meaningful and closer to a real-world setting.

Author contributions

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References

[1] Tsironis G, Zogas GC, Kyriazoglou A, et al. Breakthroughs in the treatment of advanced squamous-cell NSCLC: not the neglected sibling anymore? Ann Transl 2018;6:143.

[2] Vijayvergia N, Mehra R. Clinical challenges in targeting anaplastic lymphoma kinase in advanced non-small cell lung cancer. Cancer Chemother Pharmacol 2014;74:437–46.

[3] Back YY, Lee DK, Kim J, et al. Arg-Leu-Tyr. Glutetrapeptide inhibits tumor progression by suppressing angiogenesis and vascular permeability via VEGF receptor-2 antagonism. Oncotarget 2016;8:11763–77.

[4] Gavalas NG, Liotos M, Trachana SP, et al. Angiogenesis-related pathways in the pathogenesis of ovarian cancer. Int J Mol Sci 2013;14:15885–909.
[5] Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. Oncogene 2000;19:3548–57.
[6] Dvorak HF. Tumor stroma, tumor blood vessels, and angiogenesis therapy. Cancer J 2015;21:237–43.
[7] Al-Husein B, Abdalla M, Trepte M, et al. Angiogenic therapy for cancer: an update. Pharmacotherapy 2012;32:1093–111.
[8] Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
[9] Reck M, von PJ, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009;27:1227–34.
[10] Ding J, Chen X, Dai X, et al. Simultaneous determination of apatinib and its four major metabolites in human plasma using liquid chromatography–tandem mass spectrometry and its application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci 2012;894:896:108–15.
[11] Zhang H. Apatinib for molecular targeted therapy in tumor. Drug Des Devel Ther 2015;9:6075–81.
[12] Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 2016;34:1448–54.
[13] Hu X, Zhang J, Xu B, et al. Multicenter phase II study of apatinib, a novel VEGFR inhibitor in heavily pretreated patients with metastatic triple-negative breast cancer. Int J Cancer 2014;135:1961–9.
[14] Scott LJ. Apatinib: a review in advanced gastric cancer and other advanced cancers. Drugs 2018;78:747–58.
[15] Miao M, Deng G, Luo S, et al. A phase II study of apatinib in patients with recurrent epithelial ovarian cancer. Gynecol Oncol 2018;148:286–90.
[16] Zhang L, Shi M, Huang C, et al. A phase II, multicenter, placebo-controlled trial of apatinib in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after two previous treatment regimens. J Clin Oncol 2012;30(15_suppl):a7548.
[17] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[18] Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285:1182–6.
[19] Guo S, Colbert LS, Fuller M, et al. Vascular endothelial growth factor receptor-2 in breast cancer. Biochim Biophys Acta 2010;1806:108–21.
[20] Longo R, Gasparri N. Challenges for patient selection with VEGF inhibitors. Cancer Chemother Pharmacol 2007;60:151–70.
[21] Yang F, Tang X, Riquelme E, et al. Increased VEGFR-2 gene copy is associated with chemoresistance and shorter survival in patients with non-small cell lung carcinoma who receive adjuvant chemotherapy. Cancer Res 2011;71:5512–21.
[22] Song Z, Yu X, Lou G, et al. Salvage treatment with apatinib for advanced nonsmall-cell lung cancer. Onco Targets Ther 2017;10:1821–5.
[23] Liu Z, Ou W, Li N, et al. Apatinib monotherapy for advanced nonsmall cell lung cancer after the failure of chemotherapy or other targeted therapy. Thorac Cancer 2018;9:1285–90.
[24] Carrillo de Santa Pau E, Arias FC, Caso Peláez E, et al. Prognostic significance of the expression of vascular endothelial growth factors A, B, C, and D and their receptors R1, R2, and R3 in patients with nonsmall cell lung cancer. Cancer 2009;115:1701–12.
[25] Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J Clin Oncol 2013;31:3219–25.
[26] Li XF, Tan YN, Cao Y, et al. A case report of gastrointestinal hemorrhage and perforation during apatinib treatment of gastric cancer. Medicine (Baltimore) 2015;94:e1661.
[27] Zhou C, Wu YL, Chen G, et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. J Clin Oncol 2015;33:2197–204.
[28] Wang J, Sun Y, Liu Y, et al. Results of randomized, multicenter, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced nonsmall cell lung cancer patients. Zhong Guo Fei Ai Za Zhi 2005;8:283–90.
[29] Kosmas C, Tsavaris N, Vadiaka M, et al. Gemcitabine and docetaxel as second-line chemotherapy for patients with nonsmall cell lung carcinoma who fail prior paclitaxel plus platinum-based regimens. Cancer 2001;92:2902–10.
[30] Gao G, Jiang J, Liang X, et al. A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell lung cancer. Lung Cancer 2009;65:339–44.
[31] Schiller JH, Harrington D, Belani CP, et al. Eastern Cooperative Oncology GroupComparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.