Efficacy of Apatinib Combined with Etoposide for Maintenance Therapy in Extensive Stage Small Cell Lung Cancer

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Abstract

Objective: To investigate the efficacy, safety and survival of apatinib combined with etoposide for maintenance therapy in extensive stage small cell lung cancer (ES-SCLC).

Method: A total of 70 patients with extensive stage small cell lung cancer after standard chemo-radiotherapy who were admitted to Tangshan people's Hospital from January 2019 to February 2023 were enrolled and then grouped into the observation group and the control group by random number table method, with 35 patients in each group. Patients from the observation group received apatinib combined with oral etoposide capsules for maintenance therapy. Patients from the control group received etoposide capsules for maintenance chemotherapy. The clinical efficacy and adverse reactions of these two groups were compared, and the 6-month and 1-year survivals were followed up.

Results: The objective response rate (ORR) and disease control rate (ODC) of the observation group were higher than those of the control group [37.1% (13 / 35) vs. 17.1% (6 / 35), 65.7% (23 / 35) vs. 40% (14 / 35)], and the differences were statistically significant (all $p<0.05$). There was no significant difference in the incidence of adverse reactions between these two groups ($p>0.05$). The 6-month and 1-year survival rates of the observation group were significantly higher than those of the control group, and the differences were statistically significant (all $p<0.05$).

Conclusion: Apatinib combined with etoposide capsules applied for maintenance therapy in extensive stage small cell lung cancer could provide improved clinical efficacy and survival rate of patients, with tolerable adverse reactions.

Key words: apatinib, extensive stage small cell lung cancer, maintenance therapy, clinical efficacy.

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Introduction

Small cell lung cancer (SCLC) accounts for about 15% to 20% of all lung cancers.[1] Studies have reported that small cell lung cancer grows rapidly and is highly aggressive, and may be widely metastatic in the early stage. Most SCLC patients are diagnosed with intermediate

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and advanced stages, and more than half of them are in extensive stage.[2] Although SCLC is sensitive to radiotherapy (RT) and chemotherapy (ChT) in the early stage, treatment resistance may be easily developed in a short time, and then disease metastasis or recurrence may occur, resulting in unsatisfactory second-line treatment efficacy. Currently, neither effective targeted drugs nor maintenance therapy are available, and the prognosis is poor. Therefore, the median overall survival (OS) of ES-SCLC patients is less than 12 months, and the 5-year survival rate is less than 5%.[3,4] In recent years, molecular targeted drugs have been applied to SCLC clinic treatment to improve treatment efficacy and prognosis of patients, but significant breakthroughs on targeted therapy hasn't been achieved yet, so it is essential to find a drug with excellent curative efficacy and few adverse reactions. Vascular growth is an important part of the genesis and metastasis of tumor tissues. Due to oncogenes-induced angiogenesis, tumor tissues can obtain sufficient nutrients, leading to the rapid growth of tumor tissues. Therefore, the inhibition of angiogenesis in tumor tissues is the key to the treatment of tumor diseases.[5] Moreover, vascular endothelial growth factor (VEGF) has been proven to be closely related to the poor overall prognosis of SCLC patients, and the inhibition of VEGF is becoming a new strategy for SCLC treatment.[6] Apatinib, as a new class of oral small-molecule anti-angiogenesis drugs independently developed by China, can inhibit VEGF signaling pathway with high selectivity, thus playing an important role in retarding tumor cell growth.[7] On this basis, this study focuses on the application of apatinib combined with etoposide in maintenance therapy of small cell lung cancer, aiming to explore the efficacy, adverse reactions and impact on survival rate of apatinib in ES-SCLC maintenance therapy.

1. Subjects and Method:

1.1 Subjects

A total of 70 patients with extensive stage small cell lung cancer after standard chemoradiotherapy who were admitted to Tangshan people's Hospital from January 2019 to February 2023 were enrolled and then grouped into the observation group and the control group by random number table method, with 35 patients in each group. The observation group consisted of 20 males and 15 females, aged 45 to 69 years (with the median age of 66 years). Among them, 24 patients had primary tumors ≤ 6 cm in size, and 11 patients had primary tumors > 6 cm; as well, 21 patients had metastasis of primary tumors to one organ and 14 patients had metastasis of primary tumors to two or more organs. The control group consisted of 19 males and 16 females, aged 45 to 70 years (with the median age of 66 years). Among them, 23 patients had primary tumors ≤ 6 cm in size, and 12 patients had primary tumors > 6 cm; as well, 22 patients had the metastasis of primary tumors to one organ and 13 patients had the metastasis of primary tumors to two or more organs. There were no significant differences in gender distribution, age, primary tumor size and the number of metastatic organs between the two groups (all $p>0.05$), thus the comparative analysis could be conducted.

1.2 Inclusion and exclusion criteria

Inclusion criteria: all patients met the diagnostic criteria of small cell lung cancer [7], and were diagnosed as small cell lung cancer by cytopathological or pathological examination and further confirmed in extensive stage of SCLC by imageological examination. According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), patients after standard radiotherapy (RT) and chemotherapy (ChT) had ≥ 1 measurable lesions, with the estimated survival time of ≥ 3 months and the physical activity score of ≤ 2 points.

Exclusion criteria: patients being complicated by other types of lung cancers or other malignant tumor diseases, or with symptomatic metastases to the central nervous system, or with severe organ dysfunction or other difficult-to-control systemic diseases, or with contraindications to study drugs.

1.3 Treatment

For maintenance therapy, the control group was orally administrated with etoposide capsules at 100 mg/day for 10 consecutive days, with 21 days as a cycle; after every two cycles of chemotherapy, patients would undergo regular follow-up examinations until tumor progression. In addition to the maintenance therapy received by the control group, the observation group was orally administrated in combination with apatinib mesylate tablets (produced by Jiangsu Hengrui Pharmaceutical Co., Ltd.) at a dose of 250 mg/day on day 1 to 14 of a 21-day cycle, orally administered 30 minutes after breakfast; after every two cycles, patients would undergo regular follow-up examinations until tumor progression.

1.4 Observation indications

The clinical efficacy of the two groups were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), where complete response refers to the disappearance of all lesions after treatment; partial response refers to at least a 30% decrease in tumor diameters after treatment; stable disease refers to that tumor diameters decrease after treatment but are not enough for a partial response, or tumor diameters increase but not yet become a progressive disease; disease progression refers to the appearance of new lesions or tumor diameters increase in more than 20% after treatment; objective response rate (%) = (number of complete response cases + number of partial response cases) / total number of cases × 100%; disease control rate (%) = (number of complete response cases + number of partial response cases + number of stable disease cases) / total number of cases × 100%. According to the international evaluation system for adverse events of chemotherapeutic drugs in tumor treatment, the adverse events of these two groups were recorded, including hand foot syndrome, hypertension, proteinuria, liver injury, gastrointestinal reactions, etc. The 1-year follow-up was conducted for patients, and the survival rates of the two groups were recorded.

1.5 Statistical method

Statistical Package for Social Sciences (SPSS) software version 22.0 was used for data analysis. Count data were expressed in cases (%), and χ^2 test or Fisher exact probability test was used between groups; Kaplan Meier method was used to calculate and draw the survival curves, and Log-rank test was

used to compare the survival differences between the two groups. P<0.05 indicated a statistically significant difference.

2. Results

2.1 Comparison of clinical efficacy between two groups

In the control group, there were 1 case of complete response, 5 cases of partial response, 8 cases of stable disease and 21 cases of progressive disease, with an objective response rate of 17.1% (6/35) and a disease control rate of 40% (14/35). In the observation group, there were 3 cases of complete response, 10 cases of partial response, 10 cases of stable disease and 12 cases of progressive disease, with an objective response rate of 37.1% (13/35) and a disease control rate of 65.7% (23/35). Both the objective response rate and disease control rate of the observation group were higher than those of the control group, and the differences were statistically significant (P<0.05).

Table 1 Comparison of the objective response rate and disease control rate between two groups [n (%)]

Group	n	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)	Objective Response Rate (ORR)	Disease Control Rate (DCR)
Control	35	1 (2.85)	5 (14.3)	8 (22.9)	21 (60)	6 (17.1)	14 (40)
Observation	35	3 (8.57)	10 (28.6)	10 (28.6)	12 (34.3)	13 (37.1)	23 (65.7)
χ^2 Value						5.40	4.69
P-Value						0.02	0.03

2.2 Comparison of incidence of adverse reactions during treatment between two groups

The adverse reactions of both groups were controllable after treatment, and improvement would be made in a few patients with adverse reactions after corresponding treatment. There were no statistically significant differences in the incidence of adverse reactions between the two groups (P>0.05) (See Table 2).

2.3 Comparison of survival rates and follow-up outcomes between two groups

The 6-month and 1-year survival rates of the observation group were significantly higher than those of the control group [88.6% (31/35) vs. 65.7% (23/35), 57.1% (20/35) vs. 31.4% (11/35), respectively], and the differences were statistically significant (P<0.05). (χ^2=4.879, P=0.02).

Table 2 Comparison of adverse reactions during treatment in ES-SCLC patients after standard radiotherapy (RT) and chemotherapy (ChT) between the control group and observation group

Group	n	Hand Foot Syndrome		Hypertension		Proteinuria		Liver Injury		Gastrointestinal Reactions	
		Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Control	35	4	0	4	2	3	2	4	0	1	1
Observation	35	3	0	5	2	4	0	3	0	2	2
χ^2 Value		1.159		0.047		0.668		0.156		1.423	
P-Value		0.69		0.828		0.414		0.692		0.233	

Note: the control group was administrated with etoposide capsules for maintenance chemotherapy, while the observation group was orally administrated etoposide capsules combined with apatinib mesylate tablets

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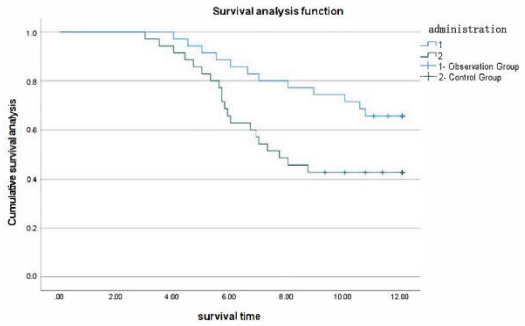

Table 3 Comparison of survival curves between the two groups.

3. Discussion

Small cell lung cancer is biologically characterized by high aggressiveness and short tumor tissue doubling time. Once diagnosed, some patients have been in extensive stage. At present, etoposide combined with cisplatin is the first-line regimen for clinical treatment of small cell lung cancer. Although the short-term effect of this regimen is good, it has a short duration of efficacy and is prone to develop drug resistance, causing disease progression or recurrence in a short time. So far, small cell lung cancer lacks therapeutic regimens or drugs for standard maintenance therapy, so it is urgent to find new regimens or drugs for follow-up treatment of small cell lung cancer.

Apatinib is a new oral small-molecule antiangiogenic drug. It was first approved mainly for use in second-line chemotherapy for gastric cancer, but a number of clinical trials have been carried out in solid tumors, including ovarian cancer, breast cancer, liver cancer and lung cancer.[8,9] Chen Ping et al reported that apatinib combined with

docetaxel was an effective and tolerable targeted drug for the treatment of advanced stage non-squamous non-small cell lung cancer.[10] According to a retrospective study on extensive stage small cell lung cancer conducted by Hong et al, among patients with relapsed and refractory small cell lung cancer who failed second-line or third-line treatment, the partial response rate and stable disease rate of patients after receiving apatinib treatment were respectively 18.2% and 30.6%, and the median progression-free survival time was 2.8 months .[11] In this study, apatinib combined with etoposide capsules were used in maintenance therapy of extensive stage small cell lung cancer until tumor progression. It was showed that the objective response rate and disease control rate of the observation group were significantly higher than those of the control group ($p<0.05$). The adverse reactions of the two groups were controllable after treatment and there was no statistically significant difference between the two groups ($p>0.05$). Thus, it could be concluded that apatinib combined with etoposide capsules for maintenance therapy could offer certain clinical benefits to ES-SCLC patients, which was consistent with previous research reports.[12]

Vascular growth plays a crucial role in not only causing tumor growth but also inducing tumor progression, invasion and metastasis.[13] Intensive researches on tumor targeted therapy contribute to the continuous discovery of various new anti-angiogenic drugs. Accordingly, the tumor anti-angiogenic therapy for tumor diseases has become increasingly important. VEGF has the ability to improve tumor survival and metastasis, and accelerates tumor growth and proliferation by activating tumor hepatocytes. Vascular endothelial growth factor receptor-2 (VEGFR-2), as a transmembrane protein mainly distributed in endothelial cells, is closely related to tumor angiogenesis. The activation of VEGFR-2 by VEGF leads to phosphorylation of VEGFR-2 at its kinase and carboxyl terminal, which maintains endothelial cell survival and accelerates the growth and metastasis of tumor tissue cells.[14,15] Apatinib, as a new oral small-molecule anti-angiogenesis drug, as well as a tyrosine kinase inhibitor targeting VEGFR2, can bind with VEGFR2 with high selectivity, block VEGFR phosphorylation, and inhibit subsequent VEGF signaling pathway, thereby exerting an inhibitory effect on tumor angiogenesis.[16] It has been confirmed that apatinib competitively inhibits the binding of VEGF and VEGFR2 by binding with VEGFR2 to block tumor cell proliferation and tumor angiogenesis, thus playing an anti-tumor role.[17] According to literature, apatinib has a more potent selective inhibitory effect on VEGFR2, compared to other tyrosine kinases inhibitors.[18] The results of this study suggest that apatinib shows encouraging anti-tumor effect by effectively inhibit vascular growth in ES-SCLC patients.

In conclusion, etoposide combined with apatinib showed a good effect on maintenance therapy of extensive stage small cell lung cancer with improved clinical efficacy and survival rate, as well as tolerable adverse reactions. The performance of overall efficacy and adverse reactions were superior than etoposide monotherapy. However, due to

the limited number of patients enrolled in this study, a large number of samples and further in-depth clinical research are required for follow-up therapy.

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