Apatinib plus chemotherapy is associated with an improved tumor response, survival and tolerance compared with chemotherapy alone for advanced lung adenocarcinoma treatment

HUA YE, WENWEN YU, YANGYANG NI, XIAOQIONG BAO, XIE ZHANG, YUNLEI LI, ALI CHEN, JIFA LI and LONG ZHENG

Department of Pulmonary and Critical Care Medicine, Yueqing People's Hospital, Yueqing, Zhejiang 325600, P.R. China

Received May 6, 2023; Accepted November 13, 2023

DOI: 10.3892/ol.2024.14327

Abstract. Apatinib plus chemotherapy demonstrates good efficacy in multiple advanced carcinomas; however, its use in patients with advanced lung adenocarcinoma (LUAD) has not yet been assessed. The present study evaluated the potential benefits of apatinib plus chemotherapy in patients with advanced LUAD. A total of 145 patients with advanced LUAD and negative driver genes who received apatinib plus chemotherapy (n=65) or chemotherapy alone (n=80) were analyzed. The overall response rate was significantly improved by apatinib plus chemotherapy vs. chemotherapy alone (53.8 vs. 36.3%; P=0.034). Moreover, progression-free survival (PFS) was significantly longer in patients who received apatinib plus chemotherapy, compared with those who received chemotherapy alone [median (95% CI), 13.4 months (11.5-15.3) vs. 8.2 months (6.9-9.5); P<0.001], as was overall survival (OS) [median (95% CI), 23.1 months (not reached) vs. 17.0 months (14.6-19.4; P=0.001). Following adjustment by multivariate Cox regression analysis, apatinib plus chemotherapy was associated with a significantly longer PFS [hazard ratio (HR), 0.444; P<0.001] and OS (HR, 0.347; P<0.001), compared with chemotherapy alone. Subgroup analyses revealed that PFS and OS were significantly improved following apatinib plus chemotherapy vs. chemotherapy alone (all P<0.05) in patients receiving first- or second-line treatment. Notably, the incidence of hypertension was significantly increased following apatinib plus chemotherapy vs. chemotherapy alone (43.1 vs. 25.0%; P=0.021), whereas the incidence of other adverse events was not significantly different between the two treatment groups (all P>0.05). In conclusion, apatinib plus chemotherapy is associated with an improved treatment response and survival compared with chemotherapy alone, with a tolerable safety profile in patients with advanced LUAD.

Correspondence to: Professor Jifa Li or Professor Long Zheng, Department of Pulmonary and Critical Care Medicine, Yueqing People's Hospital, 338 Qingyuan Road, Yueqing, Zhejiang 325600, P.R. China
E-mail: jifali8800@163.com
E-mail: linyishou8@163.com

Key words: advanced lung adenocarcinoma, apatinib plus chemotherapy, treatment response, survival profiles, adverse events

Introduction

Lung adenocarcinoma (LUAD) is the most common subtype of non-small cell lung carcinoma (NSCLC), accounting for 40-50% of cases, characterized by a high histological, cellular and molecular heterogeneity (1-3). Positive driver genes are detected in most patients with LUAD, and with the emergence of targeted therapies, the 1-year survival rates of these patients receiving targeted therapy have been improved compared with those receiving chemotherapy (24 vs. 9%) (4-8). However, ~10% of patients with advanced LUAD carry negative driver genes (9,10). According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, chemotherapy is the recommended treatment for patients with advanced LUAD carrying negative driver genes. However, certain patients do not respond well to chemotherapy, and there is a lack of effective treatment options for those patients (11,12). Therefore, exploring potential treatments for patients with advanced LUAD carrying negative driver genes is necessary.

Apatinib is an orally-administered, small-molecule vascular endothelial growth factor receptor-2 inhibitor that suppresses tumor angiogenesis (13). Recent studies have reported the potential benefit of apatinib plus chemotherapy for the treatment of advanced NSCLC (14-16). For instance, the overall remission rate has been reported to be improved by apatinib plus chemotherapy vs. chemotherapy alone in patients with advanced NSCLC (37 vs. 10%, respectively) (15). However, evidence for patients with advanced NSCLC carrying negative driver genes is scarce, and only one study has reported that the median progression-free survival (PFS; 5.47 vs. 2.97 months) and disease control rate (DCR; 95 vs. 73%) are increased following second-line apatinib plus chemotherapy compared with chemotherapy alone in patients with advanced NSCLC carrying negative driver genes (16). In addition, that study had several limitations, such as a small sample size (n=33), and it only assessed the potential of apatinib plus chemotherapy as

a second-line treatment (16). Therefore, the effect of apatinib plus chemotherapy in patients with advanced LUAD carrying negative driver genes requires further exploration.

The present study included 145 patients with advanced LUAD carrying negative driver genes to assess the efficacy and safety of apatinib plus chemotherapy compared with chemotherapy alone.

Patients and methods

Patients. A total of 145 patients with advanced LUAD who underwent treatment with either apatinib plus chemotherapy or chemotherapy alone between February 2019 and November 2022 at the Yueqing People's Hospital (Yueqing, China) were included in the present study. Specifically, 61 patients were retrospectively recruited before July 2020. Considering the number of patients was relatively small, 84 patients were prospectively recruited between July 2020 and November 2022. The inclusion criteria were as follows: i) Diagnosis of LUAD by histopathological examination; ii) >18 years; iii) presence of negative driver genes (epidermal growth factor receptor, anaplastic lymphoma kinase and reactive oxygen species proto-oncogene 1, receptor tyrosine kinase); Next-generation sequencing was carried out by 3D Medicines Inc. to identify gene mutations (17); iv) tumor-node-metastasis (TNM) stage IIIB-IV (18); v) treatment with either apatinib plus chemotherapy or chemotherapy alone; and vi) accessible and available data on clinical characteristics, treatment, radiological results and follow-up. The exclusion criteria were as follows: i) History of other malignancies prior to being diagnosed with LUAD; and ii) pregnancy or lactation. The present study was approved by the Medical Ethics Committee of Yueqing Hospital Affiliated to Wenzhou Medical University (Yueqing, China; approval no. YQYY202001003), and written informed consent was obtained from the patients or their guardians.

Next-generation sequencing. Next-generation sequencing using Illumina, Inc. technology was carried out by 3D Medicines Inc. to identify gene mutations. The kit used to prepare DNA/RNA samples for sequencing was FFPE automation (cat. no. 3103010048; 3D Medicines Inc.). The method used to verify the quality/integrity of the processed samples was Agilent 4200 (Agilent Technologies, Inc.), and the type of sequencing was double-ended, 2x150. The sequencing kit used was DNBSEQ-T7RS High-Throughput Sequencing Reagent Kit (App-A FCL PE150; version 2.0; cat. no. 940-000003-00; MGI Tech Co., Ltd.). The loading concentration of the final library was ≥33 nM measured using Qubit (Thermo Fisher Scientific, Inc.). The software used to analyze the data included: i) AdapterRemoval (version 2.3.1; https://adapterremoval.readthedocs.io/en/stable/index.html) was used for preprocessing; ii) Sentieon-bwa (version 0.7.17; https://support.sentieon.com/manual/), Sambamba (version 0.5.9; https://github.com/biod/sambamba/releases) and blat (version 35x1; DOI: 10.1101/gr.229202) were used for comparison process; iii) bedtools (version 2.25.0; https://bedtools.readthedocs.io/en/latest/index.html) was used for post-processing; and iv) Python (version 3.6.6; https://www.python.org/downloads/release/python-366/) was used for mutation detection. The raw sequencing data are not available as these were not provided by the company. The number of genes and mutations that was investigated was 35. No patient had more than one gene mutation as all patients carried negative driver genes.

Treatment regimens. Patients received apatinib plus chemotherapy or chemotherapy alone, with a mean treatment cycle of8.3 (mean treatment cycle duration, 5.8 months). The chemotherapy regimens included the following: i) docetaxel monotherapy (60-75 mg/m^2; day 1); ii) TP, paclitaxel (135-175 mg/m^2; day 1) plus cisplatin (75 mg/m^2; day 1) or carboplatin [area under the curve (AUC), 5-6 mg/ml/min; day 1]; iii) AP, pemetrexed (500 mg/m^2; day 1) plus cisplatin (75 mg/m^2; day 1) or carboplatin (AUC, 5-6 mg/ml/min; day 1); iv) DP, docetaxel (60-75 mg/m^2; day 1) plus cisplatin (75 mg/m^2; day 1) or carboplatin (AUC, 5-6 mg/ml/min; day 1); and v) pemetrexed monotherapy (500 mg/m^2; day 1). A dosage of 500 mg/day apatinib was administered and adjusted to 250 mg/day if intolerance occurred. For patients who received apatinib plus chemotherapy, apatinib was administered for maintenance treatment until the patients developed disease progression, intolerable toxicity (still uncontrolled following dosage adjustment) or death. The decision of which treatment regimen was given was based on patient willingness and physician's suggestions, and physicians were guided by the NCCN Clinical Practice Guidelines in Oncology (19).

Data collection and evaluation. Patient data on clinical characteristics, radiological results of magnetic resonance imaging or computed tomography, and follow-up were obtained. Based on the radiological information, the best response, referring to the best results from multiple assessments, was assessed using the Response Evaluation Criteria in Solid Tumors (20). At the end of the follow-up in February 2023, PFS and overall survival (OS) were determined. PFS was considered to be the interval from treatment initiation to disease progression or patient death; OS was considered to be the interval from treatment initiation to patient death. Furthermore, data on adverse events (AEs) were obtained for a safety evaluation according to Common Terminology Criteria for Adverse Events version 5.0 (21). No artificial intelligence tools were used during the present study or in the preparation of the present article.

Statistical analysis. Statistical analysis was performed using SPSS (version 24.0; IBM Corp.). Graphic rendering was completed using GraphPad Prism (version 7.0; Dotmatics). The comparison between groups was analyzed using a χ^2 test, Fisher's exact test, Wilcoxon rank-sum test or an unpaired Student's t-test. PFS and OS were determined using Kaplan-Meier curves and the log-rank test. Factors associated with PFS and OS were analyzed using Cox proportional hazards regression analysis, and multivariate Cox regression analysis was performed using the forward stepwise method. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features. Patients who received apatinib plus chemotherapy had a mean age of 57.7±9.6 years, with 32.3 and 67.7% being female and male, respectively. Patients who received

Table I. Clinical characteristics of patients with advanced lung adenocarcinoma who received either chemotherapy (n=80) or apatinib plus chemotherapy (n=65).

Characteristics	Chemotherapy, n (%)	Apatinib plus chemotherapy, n (%)	P-value
Mean age, years	60.4±9.5	57.7±9.6	0.094
Age, years			0.139
<60	32 (40.0)	34 (52.3)	
≥60	48 (60.0)	31 (47.7)	
Sex			0.515
Female	30 (37.5)	21 (32.3)	
Male	50 (62.5)	44 (67.7)	
Smoking history			0.381
No	44 (55.0)	31 (47.7)	
Yes	36 (45.0)	34 (52.3)	
ECOG PS score			0.192
0	39 (48.8)	39 (60.0)	
1	40 (50.0)	25 (38.5)	
2	1 (1.2)	1 (1.5)	
TNM stage			0.404
IIIB/C	18 (22.5)	11 (16.9)	
IV	62 (77.5)	54 (83.1)	
Bone metastasis			0.214
No	68 (85.0)	50 (76.9)	
Yes	12 (15.0)	15 (23.1)	
Brain metastasis			0.320
No	70 (87.5)	53 (81.5)	
Yes	10 (12.5)	12 (18.5)	
Treatment line			0.096
First	39 (48.8)	23 (35.4)	
Second	39 (48.8)	39 (60.0)	
Third	2 (2.4)	3 (4.6)	

Data are presented as mean ± standard deviation. ECOG PS, Eastern Cooperative Oncology Group Performance Status; TNM, Tumor-Node-Metastasis.

chemotherapy alone had a mean age of 60.4±9.5 years, with 37.5 and 62.5% being female and male, respectively. There were no significant differences in any clinical characteristics such as age and sex between patients who received apatinib plus chemotherapy and those who received chemotherapy alone (P>0.05). The detailed clinical information of these two groups of patients with advanced LUAD is listed in Table I.

Patients who received first-line apatinib plus chemotherapy had a mean age of 55.9±8.8 years, and patients who received first-line chemotherapy alone had a mean age of 59.9±9.4 years (P=0.101). There were six female patients (26.1%) and 17 male patients (73.9%) who received first-line apatinib plus chemotherapy, and there were 17 female patients (43.6%) and 22 male patients (56.4%) who received first-line chemotherapy alone (P=0.168). Notably, there were no significant differences for any of the clinical characteristics investigated between patients who received first-line apatinib plus chemotherapy and those who received first-line chemotherapy alone (P>0.05). The clinical information on patients who received either first-line apatinib plus chemotherapy or first-line chemotherapy alone is shown in Table SI.

Of those patients who received apatinib plus chemotherapy, 52.3% of patients received apatinib and docetaxel, 12.3% received apatinib and TP, 12.3% received apatinib and AP, 12.3% received apatinib and pemetrexed and 10.8% received apatinib and DP. Of those patients who received chemotherapy alone, 38.8% received docetaxel monotherapy, 20.0% received TP, 15.0% received AP, 15.0% received DP, and 11.2% received pemetrexed monotherapy (Table II).

Treatment response. The best response rate was significantly improved by apatinib plus chemotherapy compared with chemotherapy alone. In detail, the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) rates in patients who received apatinib plus chemotherapy were 1.5, 52.3, 35.4 and 10.8%, respectively, and those in patients who received chemotherapy alone were 0.0, 36.3, 42.5 and 21.3%, respectively. The overall response

Table II. Treatment regimen of patients with advanced lung adenocarcinoma receiving either chemotherapy (n=80) or apatinib plus chemotherapy (n=65).

Regimen	Chemotherapy, n (%)	Apatinib plus chemotherapy, n (%)
Docetaxel monotherapy	31 (38.8)	0 (0.0)
TP	16 (20.0)	0 (0.0)
AP	12 (15.0)	0 (0.0)
DP	12 (15.0)	0 (0.0)
Pemetrexed monotherapy	9 (11.2)	0 (0.0)
Apatinib and docetaxel	0 (0.0)	34 (52.3)
Apatinib and TP	0 (0.0)	8 (12.3)
Apatinib and AP	0 (0.0)	8 (12.3)
Apatinib and pemetrexed	0 (0.0)	8 (12.3)
Apatinib and DP	0 (0.0)	7 (10.8)

AP, pemetrexed plus platinum; DP, docetaxel plus platinum; TP, paclitaxel plus platinum.

Table III. Best response rates of patients with advanced lung adenocarcinoma receiving either chemotherapy (n=80) or apatinib plus chemotherapy (n=65).

Response rate	Chemotherapy, n (%)	Apatinib plus chemotherapy, n (%)	P-value
Best response			0.018
CR	0 (0.0)	1 (1.5)	
PR	29 (36.3)	34 (52.3)	
SD	34 (42.5)	23 (35.4)	
PD	17 (21.3)	7 (10.8)	
ORR			0.034
Yes	29 (36.2)	35 (53.8)	
No	51 (63.8)	30 (46.2)	
DCR			0.091
Yes	63 (78.8)	58 (89.2)	
No	17 (21.2)	7 (10.8)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

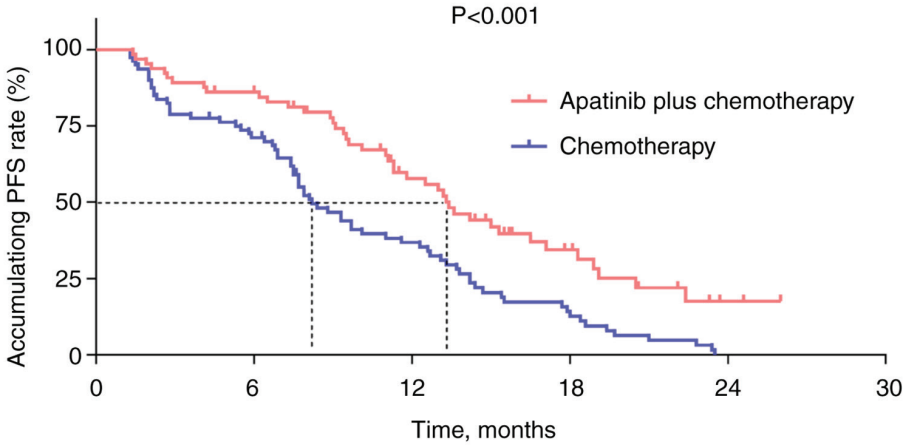
rate (ORR) was significantly improved by apatinib plus chemotherapy compared with chemotherapy alone (P=0.034), whereas there was no significant difference in DCR between groups (P=0.091; Table III).

Survival analysis. Accumulating PFS rate was significantly increased following apatinib plus chemotherapy compared with chemotherapy alone (P<0.001). The median PFS (95% CI) was 13.4 months (11.5-15.3) in patients who underwent apatinib plus chemotherapy, and 8.2 months (6.9-9.5) in patients who underwent chemotherapy alone (Fig. 1A). The accumulating OS rate was also significantly prolonged following apatinib plus chemotherapy compared with chemotherapy alone(P=0.001). The median OS (95% CI) was 23.1 months (not reached) in patients who underwent apatinib plus chemotherapy and 17.0 months (14.6-19.4) in patients who underwent chemotherapy alone (Fig. 1B).

Independent factors associated with survival. Apatinib plus chemotherapy was significantly associated with an increased PFS [hazard ratio (HR), 0.494; P<0.001]. However, sex (male vs. female; HR, 1.593; P=0.022), TNM stage (IV vs. IIIB/C; HR, 2.249; P=0.002) and higher line of treatment (HR, 1.638; P=0.005) were significantly associated with decreased PFS (Fig. 2A). Following adjustment by multivariate Cox regression analysis, apatinib plus chemotherapy was significantly independently associated with longer PFS (HR, 0.444; P<0.001), whereas higher Eastern Cooperative Oncology Group Performance Status score (22) (HR, 1.760; P=0.004), TNM stage (IV vs. IIIB/C; HR, 2.422; P=0.001) and higher line of treatment (HR, 2.081; P<0.001) were significantly independently associated with decreased PFS in patients with advanced LUAD (Fig. 2B).

Apatinib plus chemotherapy was significantly associated with increased OS (HR, 0.445; P=0.002), and higher line of

A

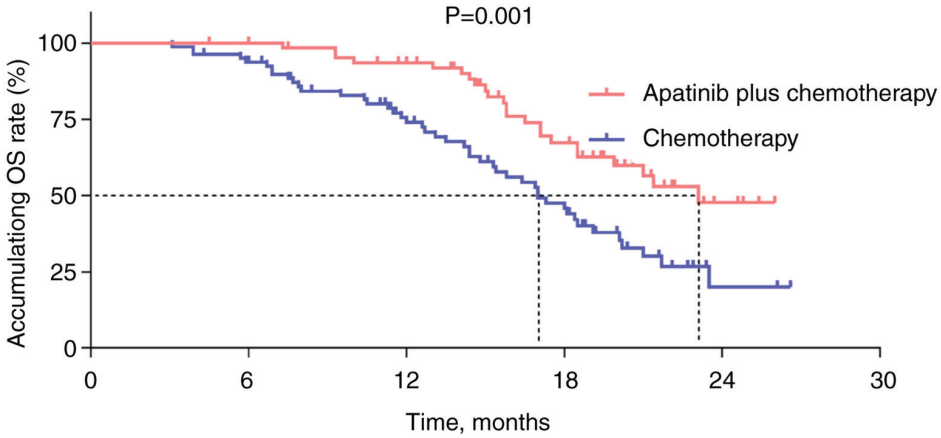


Accumulationg PFS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	86.2	57.8	34.5	17.5	17.5
Chemotherapy	100.0	71.1	36.8	12.6	0.0	0.0

	Median PFS (95% CI), months
Apatinib plus chemotherapy	13.4 (11.5–15.3)
Chemotherapy	8.2 (6.9–9.5)

B



Accumulationg OS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	100.0	93.6	67.3	47.7	47.7
Chemotherapy	100.0	93.7	74.0	45.8	20.1	20.1

	Median OS (95% CI), months
Apatinib plus chemotherapy	23.1 (not reached)
Chemotherapy	17.0 (14.6–19.4)

Figure 1. Accumulating PFS and OS rates. Comparison of (A) PFS and (B) OS between patients with advanced lung adenocarcinoma who received apatinib plus chemotherapy and those who received chemotherapy alone. PFS, progression-free survival; OS, overall survival.

treatment line was significantly associated with decreased OS (HR, 2.071; P=0.002; Fig. 3A). Following adjustment by multivariate Cox regression analysis, apatinib plus chemotherapy was significantly independently associated with longer OS (HR, 0.347; P<0.001), whereas higher line of treatment was significantly independently associated with

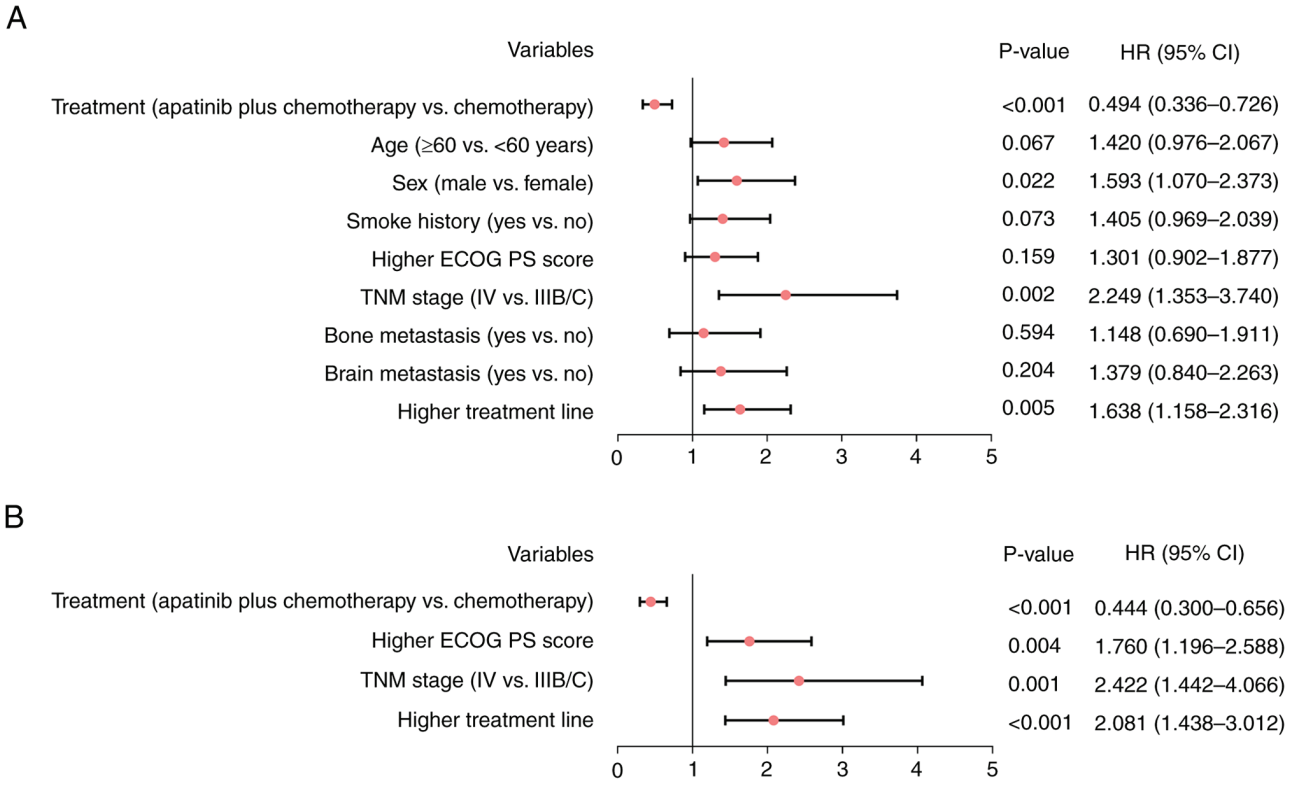


Figure 2. Independent factors related to PFS. (A) Univariate and (B) multivariate Cox proportional hazards regression analyses for PFS in patients with advanced lung adenocarcinoma. PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; TNM, Tumor-Node-Metastasis.

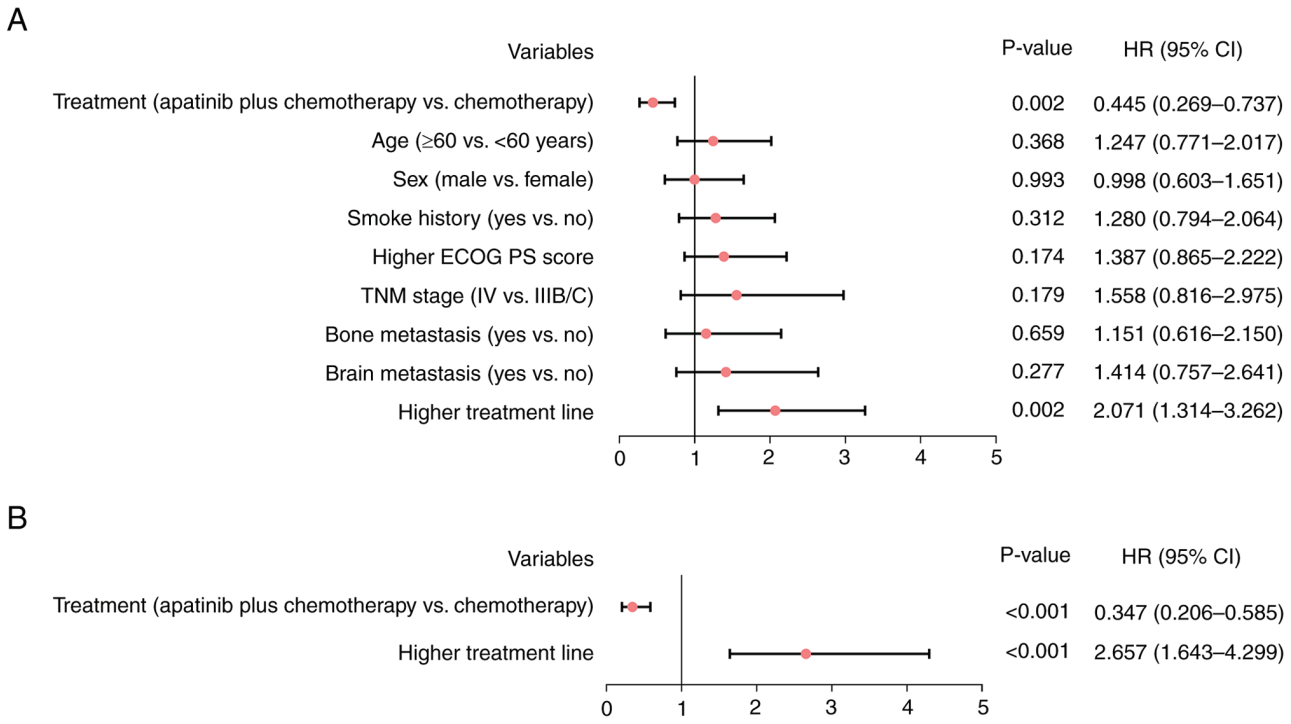
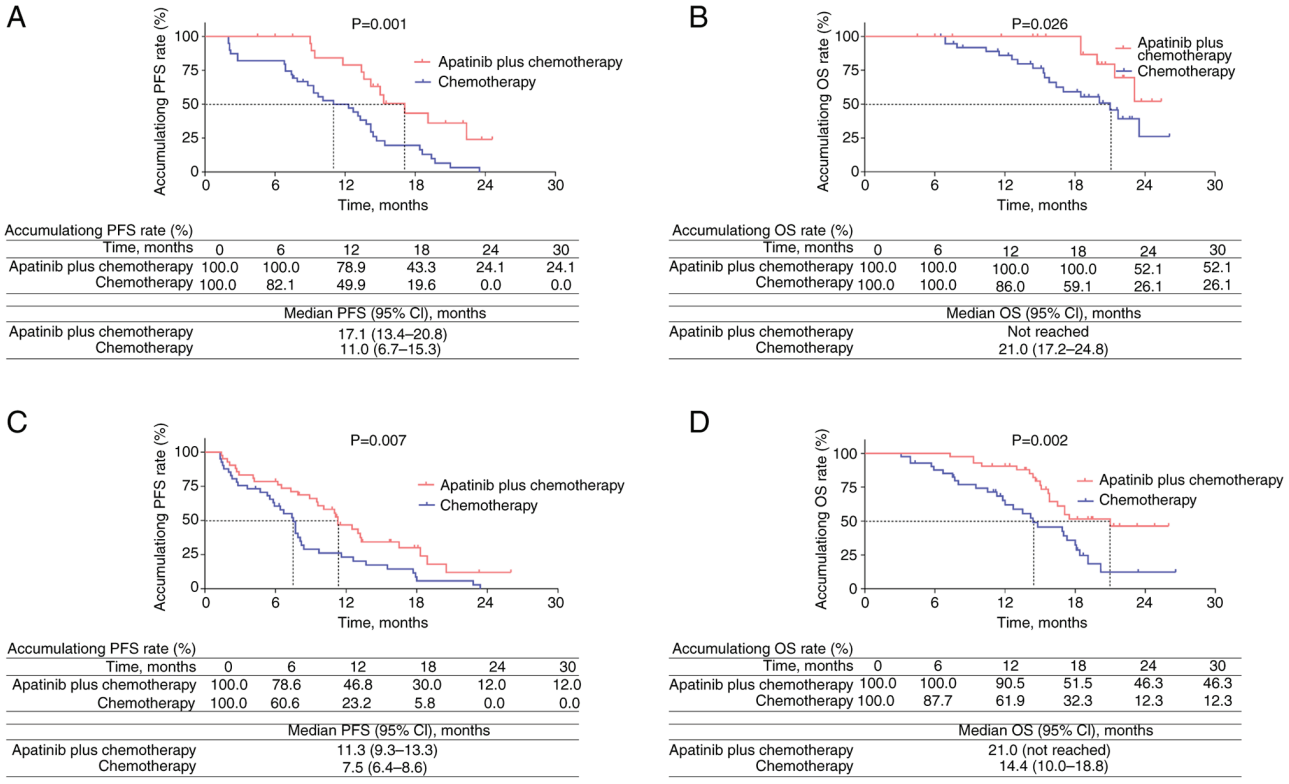


Figure 3. Independent factors related to OS. (A) Univariate and (B) multivariate Cox proportional hazards regression analyses for OS in patients with advanced lung adenocarcinoma. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; TNM, Tumor-Node-Metastasis.

reduced OS in patients with advanced LUAD (HR, 2.657; P<0.001; Fig. 3B).

Subgroup analysis of survival based on treatment lines. In patients who underwent first-line apatinib plus chemotherapy



Accumulationg PFS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	100.0	78.9	43.3	24.1	24.1
Chemotherapy	100.0	82.1	49.9	19.6	0.0	0.0

	Median PFS (95% CI), months
Apatinib plus chemotherapy	17.1 (13.4–20.8)
Chemotherapy	11.0 (6.7–15.3)

Accumulationg OS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	100.0	100.0	100.0	52.1	52.1
Chemotherapy	100.0	100.0	86.0	59.1	26.1	26.1

	Median OS (95% CI), months
Apatinib plus chemotherapy	Not reached
Chemotherapy	21.0 (17.2–24.8)

Accumulationg PFS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	78.6	46.8	30.0	12.0	12.0
Chemotherapy	100.0	60.6	23.2	5.8	0.0	0.0

	Median PFS (95% CI), months
Apatinib plus chemotherapy	11.3 (9.3–13.3)
Chemotherapy	7.5 (6.4–8.6)

Accumulationg OS rate (%)

Time, months	0	6	12	18	24	30
Apatinib plus chemotherapy	100.0	100.0	90.5	51.5	46.3	46.3
Chemotherapy	100.0	87.7	61.9	32.3	12.3	12.3

	Median OS (95% CI), months
Apatinib plus chemotherapy	21.0 (not reached)
Chemotherapy	14.4 (10.0–18.8)

Figure 4. Subgroup analyses based on the line of treatment. Comparison of (A) PFS and (B) OS between patients with advanced LUAD who received first-line treatment of apatinib plus chemotherapy treatment and those who received chemotherapy alone. Comparison of (C) PFS and (D) OS between patients with advanced LUAD who received second-line treatment or above of apatinib plus chemotherapy and those who received chemotherapy alone. PFS, progression-free survival; OS, overall survival; LUAD, lung adenocarcinoma.

or chemotherapy alone, accumulating PFS rates (P=0.001; Fig. 4A) and OS rates (P=0.026; Fig. 4B) were significantly elevated following apatinib plus chemotherapy compared with chemotherapy alone. In patients who underwent these two regimens as second-line treatment or higher, accumulating PFS rates (P=0.007; Fig. 4C) and OS rates (P=0.002; Fig. 4D) were significantly increased following apatinib plus chemotherapy compared with chemotherapy alone.

Subgroup analysis of treatment response and survival based on different chemotherapy regimens. OS was significantly prolonged by apatinib plus docetaxel compared with docetaxel alone (P=0.025), whilst ORR, DCR and PFS were not significantly affected by apatinib plus docetaxel or docetaxel alone (P>0.05). Moreover, ORR, DCR, PFS and OS were not significantly influenced by apatinib plus TP or TP alone (P>0.05). However, ORR (P=0.017) and PFS (P=0.022) were significantly prolonged by apatinib plus DP compared with DP alone. Conversely, ORR and OS were not significantly affected by apatinib plus DP or DP alone. Additionally, only PFS was significantly prolonged by apatinib plus pemetrexed compared with pemetrexed alone (P=0.017); however, ORR, DCR and OS were not significantly affected (P>0.05; Table SII).

AEs. The occurrence rate of hypertension was significantly elevated in patients who received apatinib plus chemotherapy compared with those who received chemotherapy alone (43.1 vs. 25.0%; P=0.021). However, there was no significant difference in the incidence of other AEs between patients who received the two regimens (P>0.05). In addition, the incidence of grade 3-4 AEs did not significantly differ between patients who received either treatment (P>0.05); however, the incidence of grade 3-4 AEs was relatively low in patients who received apatinib plus chemotherapy compared with those who received chemotherapy alone: i) Of those patients receiving apatinib plus chemotherapy, 13.8, 10.8, 4.6 and 3.1% experienced the grade 3-4 hematological AEs leukopenia, neutropenia, anemia and thrombopenia, respectively; and ii) of those patients receiving apatinib plus chemotherapy, 7.7, 6.2, 4.6, 4.6, 4.6 and 1.5% experienced the grade 3-4 non-hematological AEs hypertension, nausea and vomiting, elevated transaminase, anorexia, rash and hand-food syndrome, respectively (Table IV).

Discussion

Apatinib plus chemotherapy has potential benefits in treating patients with advanced NSCLC (23,24). For example, a previous study reported that 22.9% of patients with advanced NSCLC receiving apatinib plus chemotherapy achieved PR, 45.8% achieved SD and 25% achieved PD, resulting in an ORR of 29.2% and a DCR of 75.0% (24). Another previous study reported that second-line treatment or above of apatinib plus chemotherapy achieved an ORR of 33.33% in patients with advanced LUAD (23). Furthermore, the present study demonstrated that apatinib plus chemotherapy significantly increased the ORR compared with chemotherapy alone in patients with advanced LUAD. The potential reasons for this are as follows: i) Apatinib may inhibit angiogenesis and tumor growth in

Table IV. Adverse events of patients with advanced lung adenocarcinoma receiving either chemotherapy (n=80) or apatinib plus chemotherapy (n=65).

	Chemotherapy, n (%)			Apatinib plus chemotherapy, n (%)			P-value	
AE	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4	Total	Grade 3-4
Hematological								
Leukopenia	27 (33.8)	17 (21.3)	10 (12.5)	25 (38.5)	16 (24.6)	9 (13.8)	0.556	0.811
Neutropenia	25 (31.3)	18 (22.5)	7 (8.8)	22 (33.8)	15 (23.1)	7 (10.8)	0.740	0.682
Anemia	17 (21.3)	16 (20.0)	1 (1.3)	18 (27.7)	15 (23.1)	3 (4.6)	0.367	0.219
Thrombopenia	16 (20.0)	14 (17.5)	2 (2.5)	12 (18.5)	10 (15.4)	2 (3.1)	0.815	1.000
Non-hematological								
Hypertension	20 (25.0)	19 (23.8)	1 (1.3)	28 (43.1)	23 (35.4)	5 (7.7)	0.021	0.090
Hand-foot syndrome	20 (25.0)	20 (25.0)	0 (0.0)	25 (38.5)	24 (36.9)	1 (1.5)	0.081	0.448
Elevated transaminase	25 (31.3)	24 (30.0)	1 (1.3)	24 (36.9)	21 (32.3)	3 (4.6)	0.473	0.326
Nausea and vomiting	19 (23.8)	16 (20.0)	3 (3.8)	20 (30.8)	16 (24.6)	4 (6.2)	0.343	0.701
Anorexia	18 (22.5)	16 (20.0)	2 (2.5)	19 (29.2)	16 (24.6)	3 (4.6)	0.355	0.657
Alopecia	24 (30.0)	24 (30.0)	0 (0.0)	16 (24.6)	16 (24.6)	0 (0.0)	0.471	-
Diarrhea	13 (16.3)	13 (16.3)	0 (0.0)	15 (23.1)	15 (23.1)	0 (0.0)	0.300	-
Rash	14 (17.5)	12 (15.0)	2 (2.5)	15 (23.1)	12 (18.5)	3 (4.6)	0.404	0.657
Elevated bilirubin	12 (15.0)	12 (15.0)	0 (0.0)	12 (18.5)	12 (18.5)	0 (0.0)	0.577	-
Constipation	7 (8.8)	7 (8.8)	0 (0.0)	11 (16.9)	11 (16.9)	0 (0.0)	0.138	-

Statistical analysis was not performed as the occurrence of grade 3-4 AEs in both groups was 0. AE, adverse event.

LUAD, which would help improve treatment response (25-28); and ii) apatinib may have a synergistic effect with chemotherapy by sensitizing LUAD cells to chemotherapy, thereby enhancing the treatment response (15,29).

Survival is also prolonged by apatinib plus chemotherapy in patients with advanced NSCLC, according to previous studies (16,23,30). For example, a previous study reported that second-line treatment of apatinib plus chemotherapy notably increased PFS compared with chemotherapy alone (median, 5.47 vs. 2.97 months) in patients with advanced NSCLC (16). Moreover, the present study found that survival was significantly prolonged by apatinib plus chemotherapy compared with chemotherapy alone in patients with advanced LUAD, which was further demonstrated by multivariate Cox regression analysis. Notably, the median PFS was 13.4 vs. 8.2 months, and the median OS was 23.1 vs. 17.0 months in patients who received apatinib plus chemotherapy and chemotherapy alone, respectively. This may be due to the potential enhancement of the treatment response by apatinib plus chemotherapy, which may have helped further prolong the survival. In addition, subgroup analysis demonstrated that apatinib plus chemotherapy significantly prolonged survival compared with chemotherapy alone, in patients with first-line treatment and with second-line treatment or above. This finding was partly in line with that of a previous study which reported that apatinib plus docetaxel as second- or above-line treatment was effective in prolonging survival in patients with advanced non-squamous NSCLC (23). Moreover, data from the present study showed the benefit of apatinib plus chemotherapy as a first-line treatment in prolonging PFS, indicating the potential of apatinib plus chemotherapy as a first-line treatment in patients with advanced LUAD carrying negative driver genes. However, further research is required to confirm this hypothesis.

Notably, the incidence of most AEs did not significantly differ between treatments, except for hypertension, which was significantly elevated by apatinib plus chemotherapy compared with chemotherapy alone. This finding was partly in accordance with that of a previous study which indicated that the incidence of both hypertension and hand-foot syndrome were increased by apatinib plus docetaxel compared with docetaxel alone in patients with advanced NSCLC (15). Apatinib may regulate the production of nitric oxide, oxidative stress response, endothelial dysfunction and endothelin receptor 1, which are responsible for the development of hypertension (31-33). According to previous studies, the countermeasures for hypertension caused by apatinib were as follows (34-36): For patients with grade 1 hypertension [systolic blood pressure (SBP) range, 140-159 mmHg and/or diastolic blood pressure (DBP) range, 90-99 mmHg], apatinib could be continued without dose adjustment, but close monitoring of blood pressure was required (34-36); for patients with grade 2 hypertension (SBP range, 160-179 mmHg and/or DBP range, 100-109 mmHg), apatinib could be continued and usually did not need dose adjustment, but antihypertensive drugs could be applied, such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, thiazide diuretics and β-blockers (34-36); for patients with grade 3 hypertension (SBP, >180 mmHg and/or DBP, >110 mmHg), apatinib should be discontinued immediately (34-36). If treatment with a single antihypertensive drug could not control hypertension, combined antihypertensive drugs should be

considered (34-36). Although apatinib may induce hypertension, apatinib plus chemotherapy may also suit patients with underlying hypertension (35). However, the blood pressure of these patients should be controlled within the normal range before administering apatinib, and their blood pressure should be closely monitored during treatment, with timely adjustment of antihypertensive drugs in the case of an increase in blood pressure (23,24).

The present study also determined that the common AEs that occurred in patients who received apatinib plus chemotherapy were hypertension (43.1%), hand-food syndrome (38.5%), leukopenia (38.5%) and elevated transaminase (36.9%). In addition, a few grade 3-4 AEs occurred in patients with advanced LUAD. These findings were partially consistent with those of a previous study (16) which revealed that the common AEs that occurred in patients receiving apatinib plus chemotherapy were fatigue (58%), cough (39%), hand-food syndrome (38%), febrile neutropenia (23%) and hypertension (20%); meanwhile, grade 3-5 AEs rarely occurred in patients with advanced NSCLC (16). The findings demonstrated that apatinib plus chemotherapy can be effective in the treatment of patients with advanced LUAD (16,23).

Clinical evidence for the use of apatinib in the treatment of patients with advanced LUAD carrying negative driver genes is limited, and only one study has investigated the efficacy and safety of apatinib plus chemotherapy in patients with advanced NSCLC carrying negative driver genes (16). To the best of our knowledge, there is no theoretical evidence regarding the role of apatinib in NSCLC cell lines carrying negative driver genes, but, certain previous studies have assessed the synergistic effect of apatinib plus chemotherapy in general NSCLC cell lines (15,29). For instance, one study reported that apatinib investigated the effect of docetaxel in treating advanced NSCLC patients and chemoresistant NSCLC cells by regulating autophagy (15). Moreover, apatinib sensitized NSCLC cells to cisplatin by decreasing the expression of multidrug resistance protein 1 and inactivating the extracellular signal-regulated kinase pathway (29). The findings indicate that apatinib plus chemotherapy may improve the prognosis of patients with advanced NSCLC who carry negative driver genes. However, further research is required to validate the findings.

The present study had several limitations: i) It is a non-intervention study and thus, further randomized, controlled trials are required to validate its findings; ii) it is a single-center study, which may have led to selection biases; iii) apatinib was developed in China and therefore, the effect of apatinib plus chemotherapy in patients from other regions with advanced LUAD carrying negative driver genes should be assessed further.

In conclusion, apatinib plus chemotherapy is associated with a greater efficacy than chemotherapy alone, with a satisfactory safety profile in patients with advanced LUAD carrying negative driver genes. As there is a lack of effective treatment options for these patients, apatinib plus chemotherapy may have the potential to serve as a treatment option to further improve prognosis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JL and LZ contributed to the study conception and design, and provided supervision. HY and WY made contributions to data collection. YN and XB analyzed the data. XZ, YL and AC were responsible for the interpretation of data for the work. JL and LZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Yueqing Hospital Affiliated to Wenzhou Medical University (Yueqing, China; approval no. YQYY202001003), and written informed consent was obtained from the patients or their guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Seguin L, Durandy M and Feral CC: Lung adenocarcinoma tumor origin: A guide for personalized medicine. Cancers (Basel) 14: 1759, 2022.
2. Chen Z, Fillmore CM, Hammerman PS, Kim CF and Wong KK: Non-small-cell lung cancers: A heterogeneous set of diseases. Nat Rev Cancer 14: 535-546, 2014.
3. Melocchi V, Dama E, Mazzarelli F, Cuttano R, Colangelo T, Di Candia L, Lugli E, Veronesi G, Pelosi G, Ferretti GM, *et al*: Aggressive early-stage lung adenocarcinoma is characterized by epithelial cell plasticity with acquirement of stem-like traits and immune evasion phenotype. Oncogene 40: 4980-4991, 2021.
4. Tan AC and Tan DSW: Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. J Clin Oncol 40: 611-625, 2022.
5. Karimi N and Moghaddam SJ: KRAS-Mutant lung cancer: Targeting molecular and immunologic pathways, therapeutic advantages and restrictions. Cells 12: 749, 2023.
6. Kim SY, Kim SM, Lim S, Lee JY, Choi SJ, Yang SD, Yun MR, Kim CG, Gu SR, Park C, *et al*: Modeling clinical responses to targeted therapies by patient-derived organoids of advanced lung adenocarcinoma. Clin Cancer Res 27: 4397-4409, 2021.
7. Lu Y, Fan Z, Zhu SJ, Huang X, Zhuang Z, Li Y, Deng Z, Gao L, Hong X, Zhang T, *et al*: A new ALK inhibitor overcomes resistance to first- and second-generation inhibitors in NSCLC. EMBO Mol Med 14: e14296, 2022.
8. Rusdi F, Iskandar H, Hardjianti T, Bakri S, Udaya W, Kasim H, Arief E and Seweng A: The one year survival rate of lung adenocarcinoma patients treated with chemotherapy or targeted therapy. Enfermería Clínica 30: 456-460, 2020.

9. Lopez-Chavez A, Thomas A, Rajan A, Raffeld M, Morrow B, Kelly R, Carter CA, Guha U, Killian K, Lau CC, *et al*: Molecular profiling and targeted therapy for advanced thoracic malignancies: A biomarker-derived, multiarm, multihistology phase II basket trial. J Clin Oncol 33: 1000-1007, 2015.
10. Cui Y, Fang W, Li C, Tang K, Zhang J, Lei Y, He W, Peng S, Kuang M, Zhang H, *et al*: Development and validation of a novel signature to predict overall survival in 'Driver Gene-negative' Lung Adenocarcinoma (LUAD): Results of a multicenter study. Clin Cancer Res 25: 1546-1556, 2019.
11. Gao X, Chen M, Liu X, Shi Y, Liang H, Zhou Q, Zhao J, Pan R, Zhong W, Xu Y and Wang M: Prognostic factors and survival benefits of antitumor treatments for advanced non-small cell lung cancer patients with central nervous system metastasis with or without driver genes: A Chinese single-center cohort study. Front Oncol 12: 879554, 2022.
12. Hames ML, Chen H, Iams W, Aston J, Lovly CM and Horn L: Correlation between KRAS mutation status and response to chemotherapy in patients with advanced non-small cell lung cancer☆. Lung Cancer 92: 29-34, 2016.
13. Scott LJ: Apatinib: A review in advanced gastric cancer and other advanced cancers. Drugs 78: 747-758, 2018.
14. Cui YJ, Liu J, Liu MM and Zhang HZ: Observation on the clinical effect of apatinib combined with chemotherapy in the treatment of advanced non-small cell lung cancer. Pak J Med Sci 37: 1036-1041, 2021.
15. Hu R, Li T, Hui K, Chen Z, Wang N, Wu X, Ge L and Zhou L: Apatinib sensitizes chemoresistant NSCLC cells to doxetaxel via regulating autophagy and enhances the therapeutic efficacy in advanced and refractory/recurrent NSCLC. Mol Med Rep 22: 3935-3943, 2020.
16. Yu Z, Cai X, Xu Z, He Z, Lai J, Wang W, Zhang J, Kong W, Huang X, Chen Y, *et al*: Apatinib plus chemotherapy as a second-line treatment in unresectable non-small cell lung carcinoma: A randomized, controlled, multicenter clinical trial. Oncologist 25: e1640-e1649, 2020.
17. Cainap C, Balacescu O, Cainap SS and Pop LA: Next generation sequencing technology in lung cancer diagnosis. Biology (Basel) 10: 864, 2021.
18. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, *et al*: The IASLC lung cancer staging project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 12: 1109-1121, 2017.
19. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, D'Amico TA, DeCamp MM, Dilling TJ, Dobelbower M, *et al*: Non-Small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 15: 504-535, 2017.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
21. Freites-Martinez A, Santana N, Arias-Santiago S and Viera A: Using the common terminology criteria for adverse events (CTCAE – Version 5.0) to Evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 112: 90-92, 2021 (In English, Spanish).
22. Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S and Bukhari N: Performance status assessment by using ECOG (Eastern Cooperative Oncology Group) Score for cancer patients by oncology healthcare professionals. Case Rep Oncol 12: 728-736, 2019.
23. Jiang Q, Zhang NL, Ma DY, Tan BX, Hu X and Fang XD: Efficacy and safety of apatinib plus docetaxel as the second or above line treatment in advanced nonsquamous NSCLC: A multi center prospective study. Medicine (Baltimore) 98: e16065, 2019.
24. Xu J, Liu X, Yang S and Shi Y: Efficacy, safety, and prognostic factors of apatinib plus platinum doublet chemotherapy in advanced non-small cell lung cancer. J Cancer Res Ther 18: 1425-1431, 2022.
25. Huang MP, Gu SZ, Huang B, Li GW, Xiong ZP, Tang T and Zeng SN: Apatinib inhibits angiogenesis in intrahepatic cholangiocarcinoma by regulating the vascular endothelial growth factor receptor-2/signal transducer and activator of transcription factor 3/hypoxia inducible factor 1 subunit alpha signaling axis. Pharmacology 106: 509-519, 2021.
26. Song J, Guan Z, Song C, Li M, Gao Z and Zhao Y: Apatinib suppresses the migration, invasion and angiogenesis of hepatocellular carcinoma cells by blocking VEGF and PI3K/AKT signaling pathways. Mol Med Rep 23: 429, 2021.
27. Hu Y, Jing J, Shi Y, Zhang P, Dong D, Wu Y, Dong X, Li E and Fan Y: Apatinib inhibits pancreatic cancer growth, migration and invasion through the PI3K/AKT and ERK1/2/MAPK pathways. Transl Cancer Res 10: 3306-3316, 2021.
28. Xie C, Zhou X, Liang C, Li X, Ge M, Chen Y, Yin J, Zhu J and Zhong C: Apatinib triggers autophagic and apoptotic cell death via VEGFR2/STAT3/PD-L1 and ROS/Nrf2/p62 signaling in lung cancer. J Exp Clin Cancer Res 40: 266, 2021.
29. Liu ZL, Jin BJ, Cheng CG, Zhang FX, Wang SW, Wang Y and Wu B: Apatinib resensitizes cisplatin-resistant non-small cell lung carcinoma A549 cell through reversing multidrug resistance and suppressing ERK signaling pathway. Eur Rev Med Pharmacol Sci 21: 5370-5377, 2017.
30. Zhang X, Xiong Y, Xia Q, Wu F, Liu L, Zhou Y, Zeng L, Zhou C, Xia C, Jiang W, *et al*: Efficacy and safety of apatinib plus vinorelbine in patients with wild-type advanced non-small cell lung cancer after second-line treatment failure: A nonrandomized clinical trial. JAMA Netw Open 3: e201226, 2020.
31. Wang W, He Q, Li C, Zhuang C, Zhang H, Wang Q, Fan X, Qi M, Sun R and Yu J: Research on the mechanism and prevention of hypertension caused by apatinib through the RhoA/ROCK signaling pathway in a mouse model of gastric cancer. Front Cardiovasc Med 9: 873829, 2022.
32. Cohen JB, Brown NJ, Brown SA, Dent S, van Dorst DCH, Herrmann SM, Lang NN, Oudit GY, Touyz RM; American Heart Association Council on Hypertension, *et al*: Cancer therapy-related hypertension: A scientific statement from the american heart association. Hypertension 80: e46-e57, 2023.
33. Camarda N, Travers R, Yang VK, London C and Jaffe IZ: VEGF receptor inhibitor-induced hypertension: Emerging mechanisms and clinical implications. Curr Oncol Rep 24: 463-474, 2022.
34. Caletti S, Paini A, Coschignano MA, De Ciuceis C, Nardin M, Zulli R, Muiesan ML, Salvetti M and Rizzoni D: Management of VEGF-Targeted therapy-induced hypertension. Curr Hypertens Rep 20: 68, 2018.
35. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ, Ivy SP, Leier CV, Lindenfeld J, Liu G, *et al*: Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 102: 596-604, 2010.
36. Patel S, Dushenkov A, Jungsuwadee P, Krishnaswami A and Barac A: Team-Based approach to management of hypertension associated with angiogenesis inhibitors. J Cardiovasc Transl Res 13: 463-477, 2020.