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

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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.

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. QYYY202001003), 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 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 of 8.3 (mean treatment cycle duration, 5.8 months). The chemotherapy regimens included the following: i) docetaxel monotherapy (60-75 mg/m²; day 1); ii) TP, paclitaxel (135-175 mg/m²; day 1) plus cisplatin (75 mg/m²; day 1) or carboplatin [area under the curve (AUC), 5-6 mg/ml/min; day 1]; iii) AP, pemetrexed (500 mg/m²; day 1) plus cisplatin (75 mg/m²; day 1) or carboplatin (AUC, 5-6 mg/ml/min; day 1); iv) DP, docetaxel (60-75 mg/m²; day 1) plus cisplatin (75 mg/m²; day 1) or carboplatin (AUC, 5-6 mg/ml/min; day 1) and v) pemetrexed monotherapy (500 mg/m²; 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 χ² 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
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>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemotherapy, n (%)</th>
<th>Apatinib plus chemotherapy, n (%)</th>
<th>P-value</th>
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<tr>
<td>Mean age, years</td>
<td>60.4±9.5</td>
<td>57.7±9.6</td>
<td>0.094</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>&lt;60</td>
<td>32 (40.0)</td>
<td>34 (52.3)</td>
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</tr>
<tr>
<td>≥60</td>
<td>48 (60.0)</td>
<td>31 (47.7)</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.515</td>
</tr>
<tr>
<td>Female</td>
<td>30 (37.5)</td>
<td>21 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (62.5)</td>
<td>44 (67.7)</td>
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</tr>
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<td>Smoking history</td>
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<tr>
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<td>44 (55.0)</td>
<td>31 (47.7)</td>
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<tr>
<td>Yes</td>
<td>36 (45.0)</td>
<td>34 (52.3)</td>
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<td>0</td>
<td>39 (48.8)</td>
<td>39 (60.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>40 (50.0)</td>
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<td>2</td>
<td>1 (1.2)</td>
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<td>IIIB/C</td>
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<td>11 (16.9)</td>
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<tr>
<td>IV</td>
<td>62 (77.5)</td>
<td>54 (83.1)</td>
<td></td>
</tr>
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<td>Bone metastasis</td>
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<tr>
<td>No</td>
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<td>50 (76.9)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>12 (15.0)</td>
<td>15 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
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<tr>
<td>No</td>
<td>70 (87.5)</td>
<td>53 (81.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (12.5)</td>
<td>12 (18.5)</td>
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</tr>
<tr>
<td>Treatment line</td>
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</tr>
<tr>
<td>First</td>
<td>39 (48.8)</td>
<td>23 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>39 (48.8)</td>
<td>39 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>2 (2.4)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
</tbody>
</table>

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

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Table I. Clinical characteristics of patients with advanced lung adenocarcinoma who received either chemotherapy (n=80) or apatinib plus chemotherapy (n=65).
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
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
Reduced OS in patients with advanced LUAD (HR, 2.657; P<0.001; Fig. 3B).
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...
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 not only increased PFS compared with chemotherapy alone in patients with advanced NSCLC (16). 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. For patients with grade 2 hypertension [systolic blood pressure (SBP) range, 160‑179 mmHg and/or diastolic blood pressure (DBP) range, 100‑109 mmHg], 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 [systolic blood pressure (SBP) range, >180 mmHg and/or diastolic blood pressure (DBP) range, >110 mmHg], apatinib could be continued and usually did not need dose adjustment, but close monitoring of blood pressure was required. For patients with grade 4 hypertension, combined antihypertensive drugs should be used.

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

<table>
<thead>
<tr>
<th>AE</th>
<th>Chemotherapy, n (%)</th>
<th>Apatinib plus chemotherapy, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 (33.8)</td>
<td>17 (21.3)</td>
<td>10 (12.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25 (31.3)</td>
<td>18 (22.5)</td>
<td>7 (8.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (21.3)</td>
<td>16 (20.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>16 (20.0)</td>
<td>14 (17.5)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Non-hematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (25.0)</td>
<td>19 (23.8)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>20 (25.0)</td>
<td>20 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>25 (31.3)</td>
<td>24 (30.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>19 (23.8)</td>
<td>16 (20.0)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18 (22.5)</td>
<td>16 (20.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>24 (30.0)</td>
<td>24 (30.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (16.3)</td>
<td>13 (16.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (17.5)</td>
<td>12 (15.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>12 (15.0)</td>
<td>12 (15.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (8.8)</td>
<td>7 (8.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Statistical analysis was not performed as the occurrence of grade 3-4 AEs in both groups was 0. AE, adverse event.
A new ALK inhibitor overcomes therapy. Modeling clinical 

therapy may have the potential to serve as a treatment option 

treatment options for these patients, apatinib plus chemo 

satisfactory safety profile in patients with advanced LUAD 

be assessed further.

be further improved prognosis.

The present study also determined that the common AEs 

that occurred in patients who received apatinib plus chemother- 

apy 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 consist- 

tent 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 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.

In conclusion, apatinib plus chemotherapy is associated 

with a greater efficacy than chemotherapy alone, with 
asatisfactory 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 chemother- 

apy may have the potential to serve as a treatment option 
to further improve prognosis.

Acknowledgements

Not applicable.
20. cation patients by oncology healthcare professionals. Case Rep
19. Using ECOG (Eastern Cooperative Oncology Group) Score for