Efficacy and safety of bevacizumab and platinum-based chemotherapy as neoadjuvant regimen for stage-IIIA non-squamous non-small cell lung cancer: A retrospective study

DEXIONG JIANG[1], YAO RAO[1], CHUNXI ZHANG[1], DAN WANG[1], XU JIANG[1] and HUACHUAN WANG[2]

[1]Pulmonary and Critical Care Medicine, Dazhou Central Hospital, Dazhou, Sichuan 635000, P.R. China;
[2]Department of Thoracic Surgery, Dazhou Central Hospital, Dazhou, Sichuan 635000, P.R. China

Received November 30, 2023; Accepted April 26, 2024

DOI: 10.3892/ol.2024.14508

Abstract. Bevacizumab plus platinum-based chemotherapy provides modest benefits in non-squamous non-small cell lung cancer (NSCLC), while its application as a neoadjuvant regimen has yet to be validated. The present study aimed to assess the efficacy of neoadjuvant bevacizumab plus platinum-based chemotherapy in patients with stage-IIIA non-squamous NSCLC. Data from 110 patients with stage-IIIA non-squamous NSCLC with negative driver genes, who received neoadjuvant bevacizumab plus platinum-based chemotherapy (n=50) or neoadjuvant platinum-based chemotherapy alone (n=60), and tumor resection, were retrospectively reviewed in the current study. In addition, the data on pathological response, disease-free survival (DFS), overall survival (OS) and adverse events were obtained. The results demonstrated that neoadjuvant bevacizumab plus chemotherapy did not significantly increase the pathological complete response (pCR) rate in comparison with neoadjuvant chemotherapy alone (18.0 vs. 8.3%; P=0.130). However, neoadjuvant bevacizumab plus chemotherapy significantly increased the rates of DFS (P=0.007) and OS (P=0.049) compared with neoadjuvant chemotherapy alone. Adjustments were then performed using multivariate logistic or Cox regression analyses, which demonstrated that neoadjuvant bevacizumab plus chemotherapy in comparison with neoadjuvant chemotherapy alone only significantly independently prolonged DFS [hazard ratio (HR)=0.251; P=0.042], but did not significantly affect pCR (odds ratio=2.897; P=0.117) or OS (HR=0.297; P=0.158). Furthermore, no significant differences were demonstrated between the number of adverse events in patients receiving neoadjuvant bevacizumab plus chemotherapy in comparison with those receiving neoadjuvant chemotherapy alone (all P>0.05). In conclusion, neoadjuvant bevacizumab plus platinum-based chemotherapy was only associated with a significant improvement in the rate of DFS, but showed limited efficacy in improving pCR and OS rates in comparison with neoadjuvant chemotherapy alone in patients with stage-IIIA non-squamous NSCLC. Therefore, a larger sample size and randomized controlled studies are needed for further validation of the findings of the present study.

Correspondence to: Dr Huachuan Wang, Department of Thoracic Surgery, Dazhou Central Hospital, 56 Nanyuemiao Street, Tongchuan, Dazhou, Sichuan 635000, P.R. China
E-mail: 420743070@qq.com

Key words: non-squamous non-small cell lung cancer, bevacizumab, neoadjuvant therapy, efficacy, safety

Introduction

Lung cancer is a prevalent malignant tumor, with annual prevalence and age-standardized mortality rate of 87.65 and 30.2 per 100,000 individuals (1,2). Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, of which ~70% of cases are non-squamous (3,4). Notably, non-squamous NSCLC in clinical tumor-node-metastasis (cTNM) IIIA stage is a highly heterogeneous disease, and ~30-50% of patients are inoperable (5,6). At present, neoadjuvant chemotherapy is considered to increase the likelihood of surgery in inoperable patients or reduce the risk of disease recurrence, which contributes to certain survival benefits to patients with non-squamous NSCLC in cTNM IIIA stage (4,6,7). Unfortunately, current optional neoadjuvant chemotherapy regimens are relatively limited with unsatisfactory efficacy for patients with non-squamous NSCLC in cTNM IIIA stage, especially in those with negative driver genes (8). Therefore, searching for alternative neoadjuvant chemotherapy regimens is crucial to manage patients with non-squamous NSCLC in cTNM IIIA stage with negative driver genes.

Bevacizumab, as an inhibitor of vascular endothelial growth factor (VEGF), restrains growth of tumors by inhibiting angiogenesis, which is considered to contribute to the treatment of NSCLC (9,10). Notably, adjuvant bevacizumab plus platinum-based chemotherapy has provided certain clinical benefits in patients with NSCLC (11,12). For example, one study reported that adjuvant bevacizumab plus platinum-based chemotherapy reduced the recurrences of NSCLC in the brain (11). In addition, another study reported that adjuvant bevacizumab plus platinum-based chemotherapy improved overall survival (OS) to a certain extent in patients

with NSCLC (12). However, the relevant research on the application of neoadjuvant bevacizumab plus platinum-based chemotherapy in patients with NSCLC is insufficient. Several studies preliminarily assessed the efficacy of neoadjuvant bevacizumab in patients with NSCLC, which reported that bevacizumab-based regimen as neoadjuvant is feasible and safe in patients with stage III lung cancer (13,14). Furthermore, another study performed with a Chinese cohort reported that bevacizumab combined with platinum-containing neoadjuvant therapy had acceptable efficacy and safety profiles in patients with stage III lung cancer (15). However, more studies are needed to form solid conclusions on supporting the clinical usage of bevacizumab-based neoadjuvant therapy in patients with stage III lung cancer.

Therefore, the present study aimed to compare the efficacy and safety between neoadjuvant bevacizumab plus platinum-based chemotherapy and platinum-based chemotherapy alone in patients with non-squamous NSCLC in cTNM IIIA stage with negative driver genes.

Materials and methods

Subjects. The present retrospective study included 110 patients with non-squamous NSCLC who underwent neoadjuvant therapy (bevacizumab plus platinum-based chemotherapy or platinum-based chemotherapy alone) and sequential surgical resection from January 2019 to October 2022 at Dazhou Central Hospital (Dazhou, China). The inclusion criteria were as follows: i) Non-squamous NSCLC diagnosis as per the guideline from National Comprehensive Cancer Network (16); ii) presence of negative driver genes involving epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1) fusion and v-raf murine sarcoma viral oncogene homolog B1 with amino acid substitution for valine at position 600 (BRAF V600E) mutation; iii) cTNM IIIA stage; iv) bevacizumab plus platinum-based chemotherapy or platinum-based chemotherapy alone as neoadjuvant therapy received; and v) surgical resection after neoadjuvant therapy performed. The exclusion criteria were as follows: i) other malignant diseases, such as other solid tumors or hematological malignancies; ii) no available follow-up data; and iii) current pregnancy or lactation. The Ethics Committee of Dazhou Central Hospital (Dazhou, China) approved the present study (approval no. 2023100). Each subject or their guardian provided written informed consent.

Study flow. Initially, 246 patients with stage IIIA NSCLC who underwent surgical resection were screened. A total of 72 patients who had positive driver genes, 34 patients who did not receive neoadjuvant therapy, 14 patients with incomplete follow-up data, 7 patients (or their family) who could not be contacted, and 9 patients (or their family) who did not agree to participate in the study or did not provide informed consent were excluded. Subsequently, a total of 110 patients were considered eligible for analysis.

Treatment. Patients received bevacizumab plus platinum-based chemotherapy or platinum-based chemotherapy alone as neoadjuvant therapy. In the present study, the administrated regimen of platinum-based chemotherapy included: Paclitaxel-platinum (TP), liposome-encapsulated paclitaxel-platinum (LP) and pemetrexed-platinum (AP). The cycle of neoadjuvant therapy was 2-3 cycles (21-day cycle). The suggested doses were as follows: i) 7.5 mg/kg bevacizumab on the first day per cycle; ii) TP, 135-175 mg/m^2 paclitaxel + 75 mg/m^2 cisplatin or carboplatin dosed to an area under the curve (AUC) of 5.0-6.0 on the first day of each cycle; iii) LP, 135-175 mg/m^2 liposome-encapsulated paclitaxel + 75 mg/m^2 cisplatin or carboplatin dosed to an AUC of 5.0-6.0 on the first day of each cycle; iv) AP, 500 mg/m^2 pemetrexed + 75 mg/m^2 cisplatin or carboplatin dosed to an AUC of 5.0-6.0 on the first day of each cycle. Surgery was performed within 3-4 weeks after neoadjuvant therapy.

Data collection. Demographics, disease-related data and neoadjuvant therapy-linked data were collected. Simultaneously, imaging examination results of patients were collected every 2 months for the first 6 months and every 3 months thereafter. The best overall response was taken to be the best radiological response recorded during the duration of the whole treatment, which was appraised via the Response Evaluation Criteria In Solid Tumors guidelines version 1.1 (17). Subsequently, the overall response rate (ORR) was calculated. Additionally, pathological response was assessed, including major pathologic response (MPR) and pathological complete response (pCR) status. MPR was defined as ≤10% of residual viable tumor present in the resection specimen, and pCR was defined as the lack of any viable tumor cells in the resected lung cancer specimen (including all sampled regional lymph nodes) (18,19). Moreover, follow-up data (including disease status and corresponding time periods) was collected, then disease-free survival (DFS) and OS were assessed in line with it. The definition of DFS was the time from surgery to relapse or death, whilst OS was defined as the period from neoadjuvant therapy initiation to death. Furthermore, adverse events were counted for safety analysis, which was graded by the Common Terminology Criteria for Adverse Events version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Statistical analysis. Unpaired Student's t-test, χ^2 test or Mann-Whitney U test were used to perform comparison analysis according to the appropriate conditions. Kaplan-Meier curves were used to assess the DFS or OS, and the log-rank test was used to compared DFS or OS between two groups. In addition, multivariate logistic regression or Cox regression models were used to evaluate independent factors related to pCR or DFS/OS, in which the enter method (where all the factors were forced into the regression model) was used. SPSS v.26.0 (IBM Corp.) was used for data processing and GraphPad Prism v.7.0 (Dotmatics) was used for figure construction. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features. The bevacizumab plus chemotherapy group included 14 (28.0%) female and 36 (72.0%) male patients, with a mean age of 55.8±7.9 years. The chemotherapy alone group included 21 (35.0%) female and 39 (65.0%) male patients, with

Table I. Characteristics of patients with non-squamous non-small cell lung cancer.

Characteristic	Chemotherapy alone (n=60)	Bevacizumab plus chemotherapy (n=50)	P-value
Age, years	58.9±11.0	55.8±7.9	0.101
Sex			0.433
Female	21 (35.0)	14 (28.0)	
Male	39 (65.0)	36 (72.0)	
Smoking history			0.230
No	38 (63.3)	26 (52.0)	
Yes	22 (36.7)	24 (48.0)	
Histological type			0.372
Adenocarcinoma	52 (86.7)	46 (92.0)	
Others	8 (13.3)	4 (8.0)	
cT stage			0.278
cT1	0 (0.0)	3 (6.0)	
cT2	26 (43.3)	26 (52.0)	
cT3	30 (50.0)	13 (26.0)	
cT4	4 (6.7)	8 (16.0)	
cN stage			0.142
cN0	1 (1.7)	1 (2.0)	
cN1	33 (55.0)	20 (40.0)	
cN2	26 (43.3)	29 (58.0)	
cTNM stage IIIA			0.284
cT1N2M0	0 (0.0)	3 (6.0)	
cT2N2M0	26 (43.3)	26 (52.0)	
cT3N1M0	30 (50.0)	13 (26.0)	
cT4N0M0	1 (1.7)	1 (2.0)	
cT4N1M0	3 (5.0)	7 (14.0)	
ECOG PS score			0.253
0	37 (61.7)	36 (72.0)	
1	23 (38.3)	14 (28.0)	
Chemotherapy regimen			0.174
TP	36 (60.0)	22 (44.0)	
LP	18 (30.0)	18 (36.0)	
AP	6 (10.0)	10 (20.0)	

Data are presented as mean ± standard deviation or n (%). cT, clinical tumor; cN, clinical nodes; cTNM, clinical tumor-node-metastasis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TP, paclitaxel-platinum; LP, liposome-encapsulated paclitaxel-platinum; AP, pemetrexed-platinum.

a mean age of 58.9±11.0 years. Notably, there were no significant differences in baseline features between groups, such as age, clinical tumor staging and sex (all P>0.05). Characteristics of the two groups are presented in Table I. The negative driver genes defined in the present study include EGFR, ALK, ROS1 fusion and BRAF V600E mutation. All genetic mutations of the patients are listed in Table SI.

Radiological and pathological responses between groups. Complete response, partial response, stable disease and progressive disease rates in the bevacizumab plus chemotherapy group were demonstrated to be 0.0, 72.0, 28.0 and 0.0%, respectively. Meanwhile, these rates in the chemotherapy alone group were 0.0, 51.7, 45.0 and 3.3%, respectively (Fig. 1A). Notably, ORR significantly increased in the bevacizumab plus chemotherapy group compared with the chemotherapy alone group (72.0 vs. 51.7%; P=0.030; Fig. 1B).

Notably, the MPR rate was significantly increased in the bevacizumab plus chemotherapy group compared with the chemotherapy alone group (64.0 vs. 41.7%; P=0.020; Fig. 2A). However, the pCR rate was not significantly different between the bevacizumab plus chemotherapy group and the chemotherapy alone group (18.0 vs. 8.3%; P=0.130; Fig. 2B).

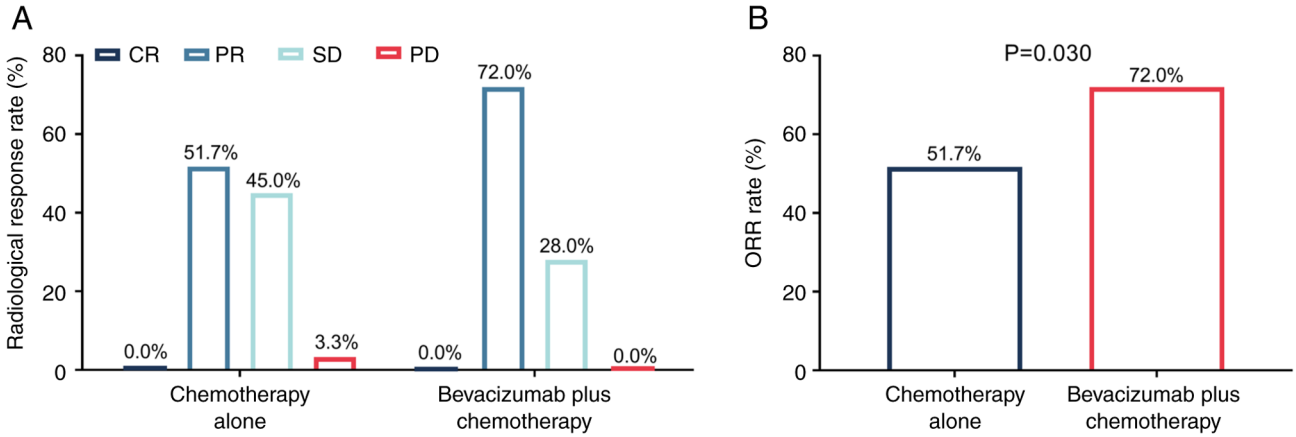

Figure 1. Radiological response between groups of patients with non-squamous non-small cell lung cancer. Comparison between the (A) radiological response and (B) ORR rates in the bevacizumab plus chemotherapy group and the chemotherapy alone group. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

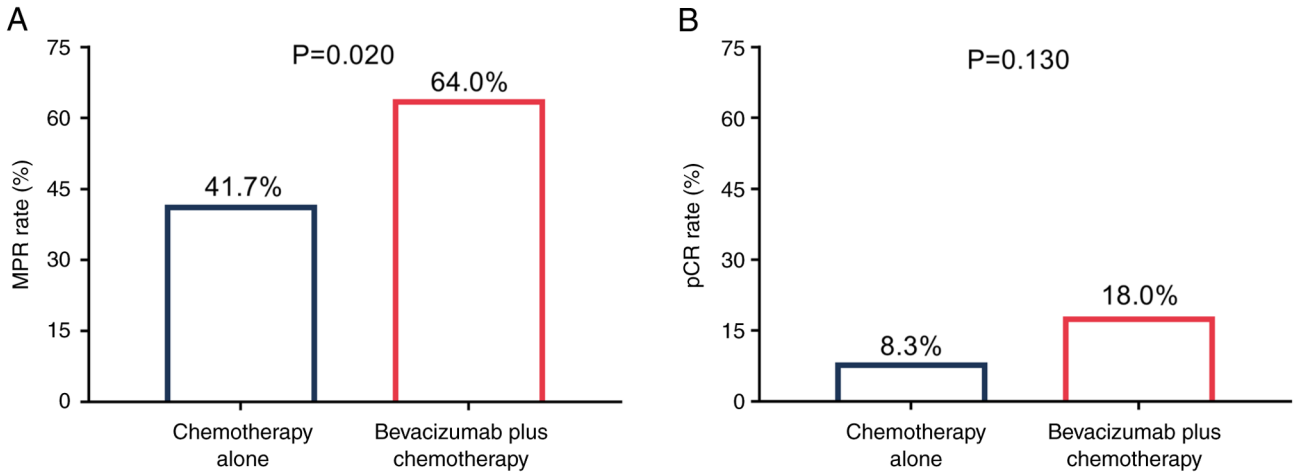

Figure 2. Pathological response between groups of patients with non-squamous non-small cell lung cancer. Comparison of (A) MPR and pCR (B) rates in the bevacizumab plus chemotherapy group and the chemotherapy alone group. MPR, major pathologic response; pCR, pathological complete response.

Factors associated with pCR. The multivariate logistic regression model revealed that bevacizumab plus chemotherapy (vs. chemotherapy alone) was not significantly independently associated with pCR in patients with non-squamous NSCLC [odds ratio (OR)=2.897; P=0.117]. The Eastern Cooperative Oncology Group Performance Status of 1 (vs. 0) was notably independently associated with a lower pCR rate in patients with non-squamous NSCLC, however this was not statistically significant (OR=0.112; P=0.053; Table II).

Accumulating DFS and OS rates between groups. The accumulating DFS rate was significantly higher in the bevacizumab plus chemotherapy group in comparison with the chemotherapy alone group (P=0.007). The 1-, 2- and 3-year accumulating DFS rates were 100.0, 91.7 and 82.5% in the bevacizumab plus chemotherapy group, respectively, and 91.9, 65.3 and 50.4% in the chemotherapy alone group, respectively (Fig. 3A). Furthermore, the accumulating OS rate was significantly higher in the bevacizumab plus chemotherapy group in comparison with the chemotherapy alone group (P=0.049). The 1-, 2- and 3-year accumulating OS rates were 100.0, 96.0 and 89.1% in the bevacizumab plus chemotherapy group, respectively, and 100.0, 81.4 and 63.4% in the chemotherapy alone group, respectively (Fig. 3B).

Factors linked with DFS and OS. Bevacizumab plus chemotherapy (vs. chemotherapy alone) was significantly independently associated with a longer DFS in patients with non-squamous NSCLC [hazard ratio (HR)=0.251; P=0.042; Table III]. However, bevacizumab plus chemotherapy (vs. chemotherapy alone) was not significantly independently associated with OS in patients with non-squamous NSCLC (HR=0.297; P=0.158; Table IV). Furthermore, all other factors were not demonstrated to be significantly independently associated with DFS or OS in patients with non-squamous NSCLC (all P>0.05; Tables III and IV).

Adverse events between groups. No significant differences were demonstrated for the number of adverse events between both groups, such as for fatigue, anemia and hand-foot syndrome (all P>0.05). In the bevacizumab plus chemotherapy group, fatigue (46.0%), alopecia (40.0%), anemia

Table II. Multivariate logistic regression model of pathological complete response in patients with non-squamous non-small cell lung cancer.

Factor	OR	95% CI	P-value
Bevacizumab plus chemotherapy vs. chemotherapy alone	2.897	(0.765-10.966)	0.117
Age, ≥60 vs. <60 years	0.608	(0.138-2.672)	0.510
Sex, male vs. female	1.751	(0.377-8.133)	0.475
Smoking history, yes vs. no	0.694	(0.181-2.661)	0.594
Histological type, adenocarcinoma vs. others	0.443	(0.061-3.195)	0.419
Higher cT stage	0.373	(0.055-2.547)	0.314
Higher cN stage	0.188	(0.014-2.591)	0.212
ECOG PS, 1 vs. 0	0.112	(0.012-1.027)	0.053
Chemotherapy regimen			
TP (reference)	1.000		
LP vs. TP	1.445	(0.400-5.222)	0.575
AP vs. TP	<0.001	(0.000-NR)	0.998

Higher cT stage (cT1<cT2<cT3<cT4) and higher cN stage (cN0<cN1<cN2) mean the hierarchical progression of stages. OR, odds ratio; CI, confidence interval; cT, clinical tumor; cN, clinical nodes; ECOG PS, eastern cooperative oncology group performance status; TP, paclitaxel-platinum; LP, liposome-encapsulated paclitaxel-platinum; AP, pemetrexed-platinum; NR, not reached.

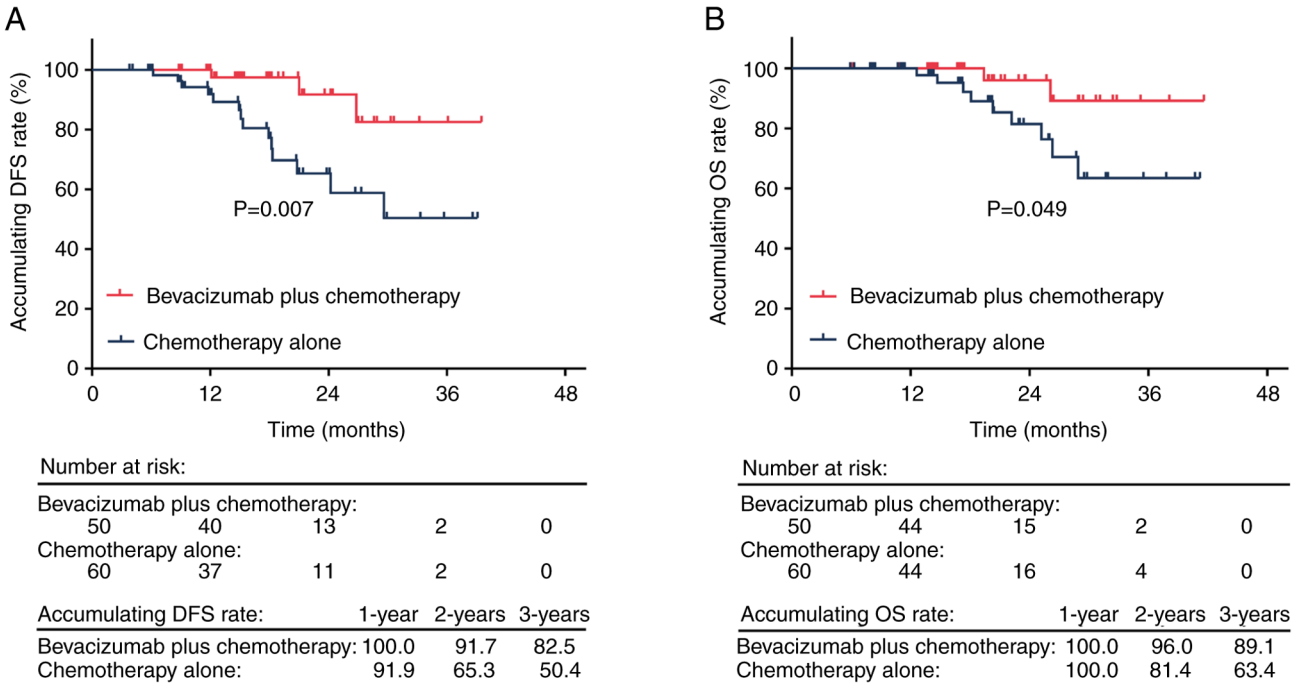

Figure 3. Accumulating DFS and OS between groups of patients with non-squamous non-small cell lung cancer. Comparison of accumulating (A) DFS and (B) OS rates in the bevacizumab plus chemotherapy group and the chemotherapy alone group. DFS, disease-free survival; OS, overall survival.

(36.0%), hand-foot syndrome (36.0%), neutropenia (36.0%), nausea and vomiting (36.0%) and hypertension (36.0%) were the most commonly reported adverse events. Moreover, in the chemotherapy alone group, alopecia (33.3%), anemia (33.3%), fatigue (30.0%), hand-foot syndrome (26.7%), neutropenia (25.0%), thrombopenia (25.0%) and nausea and vomiting (23.3%) were the most common. The incidence of hypertension was notably increased in the bevacizumab plus chemotherapy group compared with the chemotherapy alone group (36.0 vs. 20.0%), however the difference was not statistically significant (P=0.061). Furthermore, the adverse events with grade 1-2 were the most commonly reported, compared with those that were grade 3-4. Moreover, the incidence of delayed incision healing was markedly increased in the bevacizumab plus chemotherapy group compared with the chemotherapy alone group, however there was no statistically significant difference (20.0 vs. 8.3%; P=0.076; Table V).

Table III. Multivariate Cox regression model of disease-free survival in patients with non-squamous non-small cell lung cancer.

Factor	HR	95% CI	P-value
Bevacizumab plus chemotherapy vs. chemotherapy alone	0.251	(0.066-0.952)	0.042[a]
Age, ≥60 vs. <60 years	1.834	(0.558-6.029)	0.318
Sex, male vs. female	0.528	(0.139-2.006)	0.348
Smoking history, yes vs. no	1.149	(0.284-4.640)	0.846
Histological type, adenocarcinoma vs. others	0.948	(0.230-3.898)	0.941
Higher cT stage	1.858	(0.080-42.880)	0.699
Higher cN stage	5.378	(0.170-170.378)	0.340
ECOG PS, 1 vs. 0	1.454	(0.425-4.966)	0.551
Chemotherapy regimen			
TP (reference)	1.000		
LP vs. TP	0.406	(0.091-1.822)	0.239
AP vs. TP	1.975	(0.464-8.411)	0.357

Higher cT stage (cT1<cT2<cT3<cT4) and higher cN stage (cN0<cN1<cN2) mean the hierarchical progression of stages. [a]P<0.05. HR, hazard ratio; CI, confidence interval; cT, clinical tumor; cN, clinical nodes; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TP, paclitaxel-platinum; LP, liposome-encapsulated paclitaxel-platinum; AP, pemetrexed-platinum.

Table IV. Multivariate Cox regression model of overall survival in patients with non-squamous non-small cell lung cancer.

Factor	HR	95% CI	P-value
Bevacizumab plus chemotherapy vs. chemotherapy alone	0.297	(0.055-1.603)	0.158
Age, ≥60 vs. <60 years	1.263	(0.290-5.505)	0.756
Sex, male vs. female	0.363	(0.060-2.209)	0.271
Smoking history, yes vs. no	1.961	(0.309-12.453)	0.475
Histological type, adenocarcinoma vs. others	1.335	(0.232-7.668)	0.746
Higher cT stage	2.393	(0.037-155.710)	0.682
Higher cN stage	3.352	(0.035-323.152)	0.604
ECOG PS, 1 vs. 0	0.997	(0.227-4.388)	0.997
Chemotherapy regimen			
TP (reference)	1.000	-	-
LP vs. TP	0.159	(0.016-1.564)	0.115
AP vs. TP	2.008	(0.322-12.506)	0.455

Higher cT stage (cT1<cT2<cT3<cT4) and higher cN stage (cN0<cN1<cN2) mean the hierarchical progression of stages. HR, hazard ratio; CI, confidence interval; cT, clinical tumor; cN, clinical nodes; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TP, paclitaxel-platinum; LP, liposome-encapsulated paclitaxel-platinum; AP, pemetrexed-platinum.

Discussion

VEGF is an important factor for promoting angiogenesis, which participates in the progress of several cancers, such as renal carcinomas, ovarian cancer, breast cancer and NSCLC (20). Notably, bevacizumab blocks the VEGF signaling pathway, which is considered a favorable drug to suppress the growth and metastasis of NSCLC (21). At present, adjuvant bevacizumab plus platinum-based chemotherapy brings certain clinical benefits to patients with non-squamous NSCLC (11,12). For example, one study found that adjuvant bevacizumab plus platinum-based chemotherapy reduced the risk of brain metastases in patients with non-squamous NSCLC (11). Another study showed that adjuvant bevacizumab plus platinum-based chemotherapy increased OS to some extent in patients with non-squamous NSCLC (12). However, the efficacy of neoadjuvant bevacizumab plus platinum-based chemotherapy in patients with non-squamous NSCLC in cTNM IIIA stage is unclear. The present study demonstrated that neoadjuvant bevacizumab plus platinum-based chemotherapy compared with chemotherapy alone did not significantly improve the pCR in these patients. This finding agrees with that of a previous study, which reported that although neoadjuvant bevacizumab plus chemotherapy was feasible, it did not improve the pCR rate in patients with stage III NSCLC (13).

Table V. Adverse events.

	Chemotherapy alone (n=60)			Bevacizumab plus chemotherapy (n=50)			
Event	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4	P-value
Fatigue	18 (30.0)	18 (30.0)	0 (0.0)	23 (46.0)	21 (42.0)	2 (4.0)	0.084
Alopecia	20 (33.3)	20 (33.3)	0 (0.0)	20 (40.0)	20 (40.0)	0 (0.0)	0.469
Anemia	20 (33.3)	18 (30.0)	2 (3.3)	18 (36.0)	17 (34.0)	1 (2.0)	0.770
Hand-foot syndrome	16 (26.7)	16 (26.7)	0 (0.0)	18 (36.0)	18 (36.0)	0 (0.0)	0.292
Neutropenia	15 (25.0)	13 (21.7)	2 (3.3)	18 (36.0)	13 (26.0)	5 (10.0)	0.210
Nausea and vomiting	14 (23.3)	13 (21.7)	1 (1.7)	18 (36.0)	16 (32.0)	2 (4.0)	0.145
Hypertension	12 (20.0)	12 (20.0)	0 (0.0)	18 (36.0)	16 (32.0)	2 (4.0)	0.061
Leukopenia	13 (21.7)	12 (20.0)	1 (1.7)	17 (34.0)	16 (32.0)	1 (2.0)	0.148
Rash	13 (21.7)	13 (21.7)	0 (0.0)	15 (30.0)	15 (30.0)	0 (0.0)	0.318
Constipation	11 (18.3)	11 (18.3)	0 (0.0)	13 (26.0)	13 (26.0)	0 (0.0)	0.332
Elevated transaminase	11 (18.3)	10 (16.7)	1 (1.7)	13 (26.0)	12 (24.0)	1 (2.0)	0.332
Anorexia	8 (13.3)	8 (13.3)	0 (0.0)	12 (24.0)	12 (24.0)	0 (0.0)	0.149
Thrombopenia	15 (25.0)	15 (25.0)	0 (0.0)	10 (20.0)	10 (20.0)	0 (0.0)	0.533
Diarrhea	8 (13.3)	8 (13.3)	0 (0.0)	8 (16.0)	8 (16.0)	0 (0.0)	0.693
Elevated bilirubin	5 (8.3)	5 (8.3)	0 (0.0)	6 (12.0)	6 (12.0)	0 (0.0)	0.523
Delayed incision healing	5 (8.3)	NA	NA	10 (20.0)	NA	NA	0.076

Data are presented as n (%). NA, not available.

The survival rate of current neoadjuvant chemotherapy is not ideal in patients with NSCLC (22,23). For example, previous research revealed rates of 21.2 and 50.0% for 3-year DFS and OS, respectively, for patients with NSCLC in cTNM IIIA stage who were treated with neoadjuvant chemotherapy (23). Another study reported that the 3-year OS rate ranged from 58-64% in patients with NSCLC who were treated with neoadjuvant chemotherapy (22). Notably, the present study demonstrated that the 3-year DFS was 82.5%, which was higher in patients with non-squamous NSCLC in cTNM IIIA stage who received neoadjuvant bevacizumab plus platinum-based chemotherapy in comparison with those who received chemotherapy alone. The possible explanations are as follows: Bevacizumab suppressed angiogenesis by targeting the VEGF signaling pathway, thus suppressing the progression of non-squamous NSCLC (24). However, it was demonstrated that bevacizumab plus chemotherapy did not prolong OS in patients with non-squamous NSCLC in cTNM IIIA stage after adjustment by the multivariate Cox's regression analysis. This finding indicates that the efficacy of bevacizumab plus chemotherapy in patients with non-squamous NSCLC in cTNM IIIA stage is limited, and further validation is needed.

Notably, the application of bevacizumab in the treatment of patients with NSCLC may cause certain adverse events (25,26). A previous study reported that bevacizumab increased the incidences of hypertension, hemorrhagic events, leukopenia, proteinuria, febrile neutropenia and neutropenia in patients with advanced NSCLC (26). In the present study, the incidence of delayed incision healing was markedly increased in patients with non-squamous NSCLC in cTNM IIIA stage who received neoadjuvant bevacizumab plus platinum-based chemotherapy compared with those who received chemotherapy alone. This may be because bevacizumab inhibited VEGF, which prevented wound healing. Nevertheless, there was no statistical difference demonstrated. Moreover, there was no significant difference in the number of adverse events between the two groups. This may be due to the fact that the sample size was inadequate and the dose of bevacizumab was relatively low in the present study (27). Furthermore, in the neoadjuvant bevacizumab plus platinum-based chemotherapy group, grade 1-2 adverse events were the most commonly reported. These findings indicate that the safety of neoadjuvant bevacizumab plus platinum-based chemotherapy in patients with non-squamous NSCLC in cTNM IIIA stage is reliable.

In recent years, the treatment strategies of NSCLC have been continuously explored. Although neoadjuvant immunotherapy has been successful in treating patients with NSCLC to a certain extent, more neoadjuvant treatment options are required for patients with non-squamous NSCLC in cTNM IIIA stage (28). Neoadjuvant chemotherapy is still one of the predominant neoadjuvant options for the treatment of patients with NSCLC (4). Current optional neoadjuvant chemotherapy regimens report unsatisfactory efficacy in patients with non-squamous NSCLC in cTNM IIIA stage with negative driver genes (8). Notably, previous studies have reported that bevacizumab (an inhibitor of VEGF that inhibits the growth of tumors by inhibiting angiogenesis) plus platinum-based chemotherapy as a neoadjuvant chemotherapy regimen exhibits survival benefits to a certain extent in patients with non-squamous NSCLC (13-15). However, more studies are required to make a solid conclusion on supporting the clinical usage of bevacizumab-based neoadjuvant therapy in patients with stage III lung cancer.

The present study used a dose of 7.5 mg bevacizumab plus platinum-based chemotherapy as a neoadjuvant treatment regimen, and revealed that 7.5 mg bevacizumab was effective for the treatment of patients with non-squamous NSCLC in cTNM IIIA stage. This provides a potential optional treatment strategy with a low-dose of bevacizumab. Moreover, the tumor driver gene detection in the present study was based on a panel of the following genes: EGFR, Kirsten rat sarcoma viral oncogene homolog, Harvey rat sarcoma virus oncogene, neuroblastoma RAS viral oncogene homolog, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, ALK, ROS1, BRAF, human epidermal growth factor receptor 2, rearranged during transfection, tumor protein p53, mesenchymal to epithelial transition factor, mitogen-activated protein kinase kinase 1, fibroblast growth factor receptor 1 (FGFR1), FGFR2, AKT serine/threonine kinase 1, phosphatase and tensin homolog, smoothened, frizzled class receptor, KIT proto-oncogene, receptor tyrosine kinase, platelet derived growth factor receptor alpha, discoidin domain receptor 2, Retinoblastoma transcriptional corepressor 1, tuberous sclerosis complex 1, mitogen-activated extracellular signal-regulated kinase 1, breast cancer susceptibility gene, Tet methylcytosine dioxygenase 2, DNA methyltransferase 3 alpha and G protein subunit alpha 11. In the screening process of the present study, EGFR, ALK, ROS1 fusion and BRAF V600E mutation in patients with non-squamous NSCLC in cTNM IIIA stage were regarded as positive driver genes, and no mutation in any of the above four genes was demonstrated to be negative. The present study did not define the mutations of other driver genes as positive as patients with lung cancer with mutations of other driver genes lacked specific treatment drugs in Dazhou Central Hospital.

Certain limitations exist for the present study: i) Although the sample size in the present study was larger than in previous studies (13,14), future studies with an even larger sample size are required to verify the efficacy and safety of neoadjuvant bevacizumab plus platinum-based chemotherapy in patients with non-squamous NSCLC in cTNM IIIA stage; and ii) the present study is retrospective, and therefore it may have confounding factors (such as body mass index and diseases history) causing a certain degree bias.

In conclusion, neoadjuvant bevacizumab plus platinum-based chemotherapy is associated with improved DFS but has limited efficacy in improving pCR and OS rates in comparison with neoadjuvant chemotherapy alone in patients with stage-IIIA non-squamous NSCLC. Therefore, a larger sample size and randomized controlled studies are is required for further validation of the findings of the present study.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Project of Dazhou Science and Technology Bureau (grant no. 22ZDYF0020).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HW conceived and designed the study. DJ, YR, CZ, DW and XJ performed data acquisition and data analysis. DJ and HW confirm the authenticity of all the raw data. All authors wrote and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Ethics Committee of Dazhou Central Hospital approved the present study [approval no. 2023100]. Each subject or their guardian provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhu D, Shi X, Nicholas S, Ma Y and He P: Estimated annual prevalence, medical service utilization and direct costs of lung cancer in urban China. Cancer Med 10: 2914-2923, 2021.
2. Li C, Lei S, Ding L, Xu Y, Wu X, Wang H, Zhang Z, Gao T, Zhang Y and Li L: Global burden and trends of lung cancer incidence and mortality. Chin Med J (Engl) 136: 1583-1590, 2023.
3. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, *et al*: Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 497-530, 2022.
4. Chen P, Liu Y, Wen Y and Zhou C: Non-small cell lung cancer in China. Cancer Commun (Lond) 42: 937-970, 2022.
5. Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, David E, Detterbeck F, Fruh M, Gubens MA, *et al*: Management of stage III non-small-cell lung cancer: ASCO guideline. J Clin Oncol 40: 1356-1384, 2022.
6. Yoon SM, Shaikh T and Hallman M: Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol 8: 1-20, 2017.
7. Nagasaka M and Gadgeel SM: Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Expert Rev Anticancer Ther 18: 63-70, 2018.
8. Bai R, Li L, Chen X, Chen N, Song W and Cui J: Neoadjuvant and adjuvant immunotherapy: Opening new horizons for patients with early-stage non-small cell lung cancer. Front Oncol 10: 575472, 2020.
9. Zhai J, Lu J, Zhang Z, Wang Y, Li X, Zhang S, Mu S, Zhi X, Ge X, Lu D, *et al*: First-line PD-1/PD-L1 inhibitors plus chemotherapy versus bevacizumab plus chemotherapy for advanced non-squamous non-small cell lung cancer: A Bayesian network meta-analysis of randomized controlled trials. Cancer Med 11: 2043-2055, 2022.
10. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R and Chinot OL: Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev 86: 102017, 2020.
11. Varlotto JM, Wang Y, Sun Z, Wakelee HA, Ramalingam S and Schiller J: Bevacizumab's association with a decreased risk of brain metastases in ECOG-ACRIN E1505, a phase 3 randomized trial of adjuvant chemotherapy with or without bevacizumab in surgically resected NSCLC. JTO Clin Res Rep 3: 100274, 2022.
12. Wakelee HA, Dahlberg SE, Keller SM, Tester WJ, Gandara DR, Graziano SL, Adjei AA, Leighl NB, Aisner SC, Rothman JM, *et al*: Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): An open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 18: 1610-1623, 2017.
13. Chaft JE, Rusch V, Ginsberg MS, Paik PK, Finley DJ, Kris MG, Price KAR, Azzoli CG, Fury MG, Riely GJ, *et al*: Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. J Thorac Oncol 8: 1084-1090, 2013.
14. Ou W, Li N, Wang SY, Li J, Liu QW, Huang QA and Wang BX: Phase 2 trial of neoadjuvant bevacizumab plus pemetrexed and carboplatin in patients with unresectable stage III lung adenocarcinoma (GASTO 1001). Cancer 122: 740-747, 2016.
15. Xie N, Qu YZ, Jiang HP and Yang XJ: Effect of preoperative of bevacizumab combined with platinum-containing neoadjuvant chemotherapy on the prognosis of patients with stage IIIA-N2 stage lung cancer surgery. Chin J Surg Oncol 14: 371-375, 2022.
16. 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.
17. 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.
18. Travis WD, Dacic S, Wistuba I, Sholl L, Adusumilli P, Bubendorf L, Bunn P, Cascone T, Chaft J, Chen G, *et al*: IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. J Thorac Oncol 15: 709-740, 2020.
19. Pataer A, Weissferdt A, Correa AM, Vaporciyan AA, Sepesi B, Heymach JV, Berezowska S, Cascone T and Swisher SG: Major pathologic response and prognostic score predict survival in patients with lung cancer receiving neoadjuvant chemotherapy. JTO Clin Res Rep 3: 100420, 2022.
20. Mabeta P and Steenkamp V: The VEGF/VEGFR axis revisited: Implications for cancer therapy. Int J Mol Sci 23: 15585, 2022.
21. Le X, Nilsson M, Goldman J, Reck M, Nakagawa K, Kato T, Ares LP, Frimodt-Moller B, Wolff K, Visseren-Grul C, *et al*: Dual EGFR-VEGF pathway inhibition: A promising strategy for patients with EGFR-mutant NSCLC. J Thorac Oncol 16: 205-215, 2021.
22. Dell'Amore A, Lomangino I, Tamburini N, Bongiolatti S, Parri NSF, Grossi W, Catelli C, Lorenzoni G, Gregori D, Nicotra S, *et al*: Video-assisted thoracoscopic lobectomy after neoadjuvant chemotherapy for non-small cell lung cancer: A multicenter propensity-matched study. Surg Endosc 36: 1466-1475, 2022.
23. Zhao L, Zhang L, Gong F and Xu J: Thoracoscopic radical resection in the treatment of NSCLC patients (stage IIIA) after neoadjuvant chemotherapy. J BUON 26: 313-319, 2021.
24. Trukhin D, Poddubskaya E, Andric Z, Makharadze T, Bellala RS, Charoentum C, Yanez Ruiz EP, Fulop A, Hyder Ali IA, Syrigos K, *et al*: Efficacy, safety and immunogenicity of MB02 (bevacizumab biosimilar) versus reference bevacizumab in advanced non-small cell lung cancer: A randomized, double-blind, phase III study (STELLA). BioDrugs 35: 429-444, 2021.
25. Quintanilha JCF, Wang J, Sibley AB, Jiang C, Etheridge AS, Shen F, Jiang G, Mulkey F, Patel JN, Hertz DL, *et al*: Bevacizumab-induced hypertension and proteinuria: A genome-wide study of more than 1000 patients. Br J Cancer 126: 265-274, 2022.
26. Liu Y, Li HM and Wang R: Effectiveness and safety of adding bevacizumab to platinum-based chemotherapy as first-line treatment for advanced non-small-cell lung cancer: A meta-analysis. Front Med (Lausanne) 8: 616380, 2021.
27. Zhou CH, Yang F, Jiang WJ, Zhang YC, Yang HY, Zeng L, Liu L, Xiong Y, Zeng FX, Wang Z and Yang N: Efficacy and safety of different doses of bevacizumab combined with pemetrexed and platinum in first-line treatment of advanced NSCLC: A retrospective-real world study. Front Pharmacol 12: 727102, 2021.
28. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, DeCamp M, *et al*: NCCN guidelines® insights: Non-small cell lung cancer, version 2.2023. J Natl Compr Canc Netw 21: 340-350, 2023.