ORIGINAL RESEARCH

Absolute Neutrophil Count in the Peripheral Blood Predicts Prognosis in Lung Cancer Patients Treated with Anlotinib

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Purpose: Anlotinib is a multi-targeted tyrosine kinase inhibitor that inhibits tumor angiogenesis and cell proliferation. It is widely used as a third-line therapy for lung cancer. However, reliable prognostic biomarkers for predicting the efficacy of anlotinib are lacking. We conducted a retrospective study to investigate the prognostic value of serological inflammatory biomarkers in anlotinib treatment.

Patients and Methods: Patients with advanced lung cancer treated with anlotinib monotherapy were enrolled. Cox regression was conducted to analyze the significant factors related to progression-free survival (PFS) and overall survival (OS). The objective response rate (ORR) was compared based on the median cut-off value of the significant inflammation index. Meanwhile, we created survival curves to compare the two groups and performed receiver operating characteristic curve analysis to assess the predictive ability of the inflammation index.

Results: Among a total of 71 patients, the median PFS was 5.5 months and the median OS was 9.5 months. The ORR and disease control rate were 16.9% and 84.5%, respectively. According to univariate and multivariate analyses, absolute neutrophil count (ANC) was the only indicator associated with both PFS (hazard ratio [HR] =1.095, 95% confidence interval [CI] 1.030–1.163, P=0.003) and OS (HR=1.057, 95% CI 1.003–1.113, P=0.037). In the group with ANC ≥4.58, the ORR was relatively lower (8.1% vs 26.5%, P=0.057), but not statistically significant; PFS and OS were relatively shorter (median PFS 5.0 [95% CI 4.4–9.6] vs 7.0 months [95% CI 4.4–5.7], P=0.024 and median OS 7.3 [95% CI 4.7–10.0] vs 17.6 months [95% CI 12.3–22.9], P < 0.001). ANC had a relatively high discriminatory ability to predict 10-month survival, with an area under the curve of 0.729, sensitivity of 82.5%, and specificity of 67.7%.

Conclusion: Elevated pre-treatment ANC was associated with a poor prognosis. Patients with lower peripheral blood levels of ANC might benefit from anlotinib.

Keywords: lung cancer, anlotinib, absolute neutrophil count, progression-free survival, overall survival

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. According to Global Cancer Statistics in 2020, there were an estimated 2.2 million new lung cancer cases and 1.8 million deaths, accounting for about 11.4% of newly diagnosed cancers and 18.0% of deaths.[1] In terms of histopathology, lung cancer is usually classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In case of NSCLC, approximately 75% of the patients are already at an

advanced stage upon diagnosis, with a 5-year survival rate of <15%;[2] SCLC is characterized by an aggressive clinical course, with a 5-year overall survival (OS) of 20–25% for early-stage disease and 2% for extended disease.[3] Currently, in addition to conventional chemotherapy, the emergence of targeted therapy based on genomic medicine and immunotherapy based on immunological checkpoint inhibitors has significantly improved the quality of life and survival time of patients.[4] Antiangiogenic drugs are also considered to have promising therapeutic effects, especially in patients who cannot tolerate chemotherapy, those with untreatable gene mutations or with pathologically confirmed immunologically-cold tumors.[5]

Anlotinib is a newly developed oral multi–targeted tyrosine kinase receptor inhibitor that targets the vascular endothelial growth factor receptor (VEGFR) 1–3, c-Kit, platelet-derived growth factor receptor–α, and fibroblast growth factor receptor 1–4. It can inhibit both tumor angiogenesis and tumor cell proliferation.[6,7] In recent years, two randomized, double-blind, placebo-controlled, multicenter, Phase II/III trials comparing the efficacy and safety of anlotinib with that of placebo in refractory NSCLC patients who progressed after at least two lines of prior treatments have revealed its efficacy.[8,9] In China, anlotinib is one of the most common antiangiogenic drugs used in lung cancer treatment. However, not all patients with advanced lung cancer will benefit from anlotinib and the predictive biomarkers to select suitable patients are insufficient. Although clinical trials have identified some biomarkers as predictors of anlotinib activity, such as activated circulating endothelial cells, epidermal growth factor receptor (EGFR)-sensitizing mutations, and the T790M mutation,[10] these markers are not universal and are expensive. Hence, there is a considerable need to identify feasible prognostic biomarkers for anlotinib therapy.

Peripheral blood-based inflammatory parameters, such as C-reactive protein (CRP), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) are readily available in the clinic. These parameters and their composite indicators, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have shown prognostic value in a spectrum of malignancies and could predict outcomes of patients with platinum–based chemotherapy, nivolumab treatment, and bevacizumab therapy.[11–16] To date, no study has focused on the correlation between peripheral blood-based inflammatory parameters and the therapeutic efficacy of anlotinib treatment. Thus, we conducted a retrospective study to explore the predictive value of candidate inflammatory biomarkers in patients with lung cancer treated with anlotinib.

Materials and Methods
Study Design and Patient Selection
A total of 181 patients who had advanced lung cancer and were treated with anlotinib (one cycle of 12 mg daily for 14 days, then discontinued for 7 days, and repeated every 21 days) in Ruijin Hospital between July 2018 and February 2020 were screened. All patients were diagnosed with lung cancer according to histopathological criteria (World Health Organization, 2015). Patients in advanced or recurrent stage IIIA–B/IV based on the TNM classification (version 7) with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 were enrolled initially. Patients with concomitant infections, including human immunodeficiency virus and hepatitis, or those receiving systemic steroids before anlotinib treatment were excluded. Finally, 71 patients with complete clinical data and treatment with anlotinib monotherapy were included in the study. From the first dose of anlotinib, all patients were followed up for at least 10 months. Since this was a retrospective study that only analyzed the clinical data in the patient's medical records, informed consent was formally waived by the Ethics Committee of Ruijin Hospital. This study was conducted in accordance with the Declaration of Helsinki, and all patient information was kept confidential.

Data Collection
We gathered data on demographics, clinicopathological characteristics, distant metastases, gene mutations, and previous treatment lines from the electronic medical records. Complete blood cell counts were performed at baseline within a week prior to the first dose of anlotinib. We collected baseline data on serological markers of inflammation, including CRP, ANC, and ALC.

Study Assessments
Therapeutic effects were assessed using the Response Evaluation Criteria in Solid Tumors version 1.1, by performing computed tomography scans and nuclear magnetic resonance imaging every 2 months or when the clinical symptoms worsened. Progression-free survival (PFS) was defined as the duration from the beginning of anlotinib administration to tumor progression or death. Objective tumor responses consisted of complete response (CR), partial response (PR), stable disease (SD), and

progressive disease (PD). The objective response rate (ORR) included the CR and PR, and the disease control rate (DCR) included CR, PR, and SD. The 10-month survival was defined as the time from the first day of anlotinib treatment to death or the last follow-up of 10 months.

Statistical Analysis

Categorical variables were reported as frequencies with percentages, and continuous variables were described as medians with interquartile range (IQR). Significant factors related to PFS and OS were estimated using univariate and multivariate Cox regression analyses. According to the median ANC, patients were divided into relatively high and low level groups. The Log rank test was used for the analysis of PFS and OS and survival curves were created using the Kaplan–Meier method. The response to anlotinib between the two groups was compared using the Pearson χ^2 or Fisher's exact test. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to assess the ability of ANC to predict the 10-month survival. The level of significance for all statistical tests was set at a two-sided P value of 0.05. Statistical analyses were performed using the SPSS Version 25.0 statistical software (IBM Corporation, Armonk, NY, USA).

Results
Patient Characteristics

Based on the inclusion and exclusion criteria, 71 patients with relatively complete clinical, pathological and follow-up data were included in the study (Figure 1). The average age of the patients was 68±9 years with a male predominance (71.8%). A total of 45 patients (63.4%) had a smoking history and 70 patients (79.5%) had an ECOG PS of 0. Overall, 49 patients (69.0%) had adenocarcinoma, 14 (57.7%) had squamous cell carcinoma, 7 (9.9%) had small cell lung cancer, and 1 (1.4%) had another histologic type. Brain metastasis accounted for 11.3% of the metastatic sites, liver metastasis for 2.8%, and bone metastasis for 28.2%. Additionally, 61 patients (85.9%) had lymphatic metastasis. Stage IV disease was present in 56 patients (78.9%), with 12 (16.9%) having more than one metastatic site. *EGFR* mutations were identified in 7 patients (9.9%). Regarding treatment, 54 patients (76.0%) received palliative chemotherapy, 18 (25.4%) received radiation therapy, 27 (38.0%) received targeted therapy, and 1 (1.4%) received PD-1 inhibitor treatment prior anlotinib treatment. More than three prior lines of therapy were noted in 28 patients (39.4%). The median CRP, ANC, and ALC were 12.0 mg/L (IQR, 3.0–48.3), 4.6 (IQR, 3.7–6.3), and 1.3 (IQR, 0.9–1.7), respectively. The characteristics of all patients are listed in Table 1.

Survival Outcomes

For the patients included in the analysis, the median PFS (mPFS) was 5.5 months (IQR, 4.0–8.0) and median OS (mOS) was 9.5 months (IQR, 6.0–3.4). According to univariate analysis, number of prior lines of therapy > 3 (hazard ratio [HR]= 1.735; 95% confidence interval [CI] 1.013–2.974, P=0.045) and higher levels of ANC (HR=1.105; 95% CI
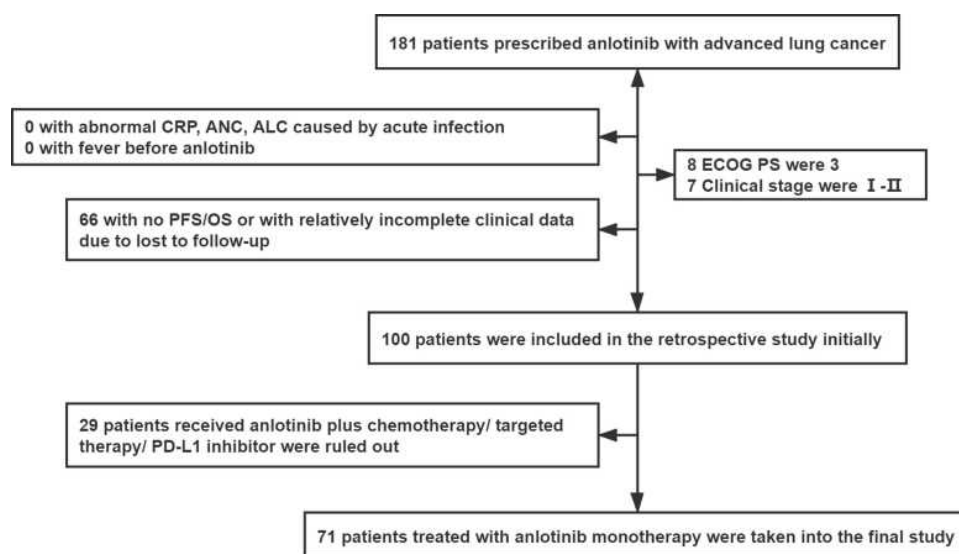

Figure 1 Flowchart of the study participants.

Table I Baseline Characteristics of Study Participants

Gender, N (%)	Male	51 (71.8)
	Female	20 (28.2)
Age at start anlotinib (years)	Average±SD	68± 9
Tobacco, N (%)	Never smoker	26 (36.6)
	Current smoker	38 (53.5)
	Former smoker	7 (9.9)
ECOG PS, N (%)	0	49 (69.0)
	I	22 (31.0)
Histologic type, N (%)	Squamous cell carcinoma	14 (57.7)
	Adenocarcinoma	49 (69.0)
	Small cell lung cancer	7 (9.9)
	Other	I (1.4)
Metastasis sites, N (%)	Brain	8 (11.3)
	Liver	2 (2.8)
	Bone	20 (28.2)
	No	7 (9.9)
Lymphatic metastasis	Yes	61 (85.9)
	No	10 (14.1)
Number of metastatic sites, N (%)	≤ I	59 (83.1)
	> I	12 (16.9)
Clinical stage, N (%)	IIIA-IIIB	15 (21.1)
	IV	56 (78.9)
Gene mutation, N (%)	*EGFR* mutation	7 (9.9)
	Wild type	64 (90.1)
Prior lines of therapy, N (%)	≤ 3	43 (60.6)
	> 3	28 (39.4)
Previous therapy, N (%)	Chemotherapy	54 (76.0)
	Radiation therapy	18 (25.4)
	Targeted treatment	27 (38.0)
	PD–I inhibitor	I (1.4)
CRP, mg/L[a]	Median (IQR)	12.0 (3.0–48.3)
ANC (×10⁹/L)	Median (IQR)	4.6 (3.7–6.3)
ALC (×10⁹/L)	Median (IQR)	1.3 (0.9–1.7)

Note: [a]Data were missing in three patients.
Abbreviations: EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein-1; CRP, C–reactive protein; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; SD, standard deviation; IQR, interquartile range.

1.044–1.170, P=0.001) were associated with a shorter PFS, while age ≥ 65 years (HR=1.881; 95% CI 1.041–3.397, P=0.036), tobacco use (HR=1.854; 95% CI 1.012–3.398, P=0.046), and higher ANC (HR=1.070; 95% CI 1.023–1.121, P=0.004) were associated with a shorter OS. We fitted

multivariable Cox regression models using age ≥ 65, tobacco use, number of prior lines of therapy, and ANC. Ultimately, only high ANC values were found to contribute significantly to the prediction of PFS (HR= 1.095, 95% CI 1.030–1.163; P=0.003) and OS (HR= 1.057, 95% CI 1.003–1.113; P=0.037). The univariate and multivariate Cox analyses are shown in Tables 2 and 3.

Co-Relation Between ANC and Prognosis

Regarding the result of the multivariable analysis, ANC was associated with the PFS and OS in patients treated with anlotinib. Therefore, we divided the patients into two groups according to median ANC values for further verification. There were no statistical differences in the demographics and clinical characteristics between the two groups, except for the ECOG PS (Supplementary Table 1). According to the assessment, the responses among the patients treated with anlotinib were PR (n=12), SD (n=48), and PD (n=11). The ORR and DCR were 16.9% and 84.5%, respectively. Higher baseline ANC (ANC ≥ 4.58) was associated with a lower ORR, although there were no statistically significant differences between the two groups (26.5% vs 8.5%, P=0.057). Using the Log rank test, we also found that ANC ≥ 4.58 demonstrated inferior mPFS (5.0 [95% CI 4.4–5.7] vs 7.0 months [95% CI 4.4–9.6], P=0.024; Figure 2) and mOS (7.3 [95% CI 4.7–10.0] vs 17.6 months [95% CI 12.3–22.9], P<0.001; Figure 3). The detailed analysis is shown in Table 4.

Predictive Ability of ANC

To better analyze the predictive ability of ANC, we used "10-month survival" as the outcome to establish the predictive model. Based on ROC curve analysis (Figure 4), the AUC for ANC was 0.729 (95% CI 0.603–0.854; P=0.001). With an optimal cut-off of 4.32, the sensitivity and specificity for predicting 10-month mortality were 82.5% and 67.7%, respectively.

Discussion

This was a retrospective study that aimed to determine the role of some inflammatory parameters in the peripheral blood in predicting the survival of patients with lung cancer who received anlotinib therapy. According to the results of univariate and multivariate analyses, ANC was related to the patient outcome. A higher baseline ANC was significantly associated with a shorter PFS and OS. ANC may also be a predictive biomarker for 10-month mortality.

Table 2 Univariate Cox Regression Analyses of PFS and OS

Variable	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age ≥ 65 (vs Age < 65 years old)	1.182	0.696–2.007	0.536	1.881	1.041–3.397	0.036*
Male (vs female)	1.264	0.708–2.256	0.428	1.312	0.694–2.482	0.403
Squamous (vs other)	1.149	0.607–2.174	0.669	1.504	0.761–2.974	0.240
Adenocarcinoma (vs other)	1.009	0.577–1.765	0.974	0.816	0.449–1.484	0.506
ECOG PS at treatment start	1.085	0.614–1.917	0.779	1.573	0.895–2.766	0.115
Tobacco use (vs none)	1.206	0.703–2.068	0.497	1.854	1.012–3.398	0.046*
Liver metastasis (vs none)	0.909	0.125–6.608	0.925	2.440	0.586–10.154	0.220
Skeletal metastasis (vs none)	1.051	0.593–1.861	0.865	0.799	0.421–1.514	0.491
Brain metastasis (vs none)	0.539	0.213–1.364	0.192	0.607	0.236–1.562	0.300
Lymphatic metastasis (vs none)	0.674	0.339–1.339	0.260	1.314	0.557–3.095	0.533
IV Stage (vs IIIA–IIIB Stage)	0.824	0.443–1.531	0.540	0.638	0.331–1.229	0.179
EGFR mutation (vs non–EGFR mutation)	1.395	0.629–3.096	0.413	0.902	0.356–2.286	0.829
No. of previous treatment lines > 3 (vs ≤ 3)	1.735	1.013–2.974	0.045*	1.112	0.634–1.950	0.710
Previous chemotherapy (vs with no previous therapy)	1.301	0.654–2.587	0.453	0.788	0.386–1.610	0.513
Previous targeted therapy (vs with no previous therapy)	1.463	0.791–2.706	0.226	1.835	0.928–3.626	0.081
Previous targeted therapy (vs with no previous therapy)	1.376	0.798–2.371	0.251	1.120	0.619–2.027	0.708
Previous PD–1 inhibitor (vs with no previous therapy)	1.581	0.216–11.583	0.652	2.658	0.357–19.77	0.340
CRP[a]	1.002	0.997–1.006	0.479	1.003	0.998–1.007	0.250
ANC	1.105	1.044–1.170	0.001*	1.070	1.023–1.121	0.004*
ALC	0.841	0.567–1.249	0.391	0.862	0.553–1.346	0.515

Note: [a]Data were missing in three patients. *$p < 0.05$.
Abbreviations: EGFR, epidermal growth factor receptor; PD-L1, programmed cell death protein ligand-1; CRP, C–reactive protein; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; HR, hazard ratio; CI, confidence interval.

Table 3 Multivariate Cox Regression Analysis of PFS and OS

Variable	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age ≥ 65 (vs Age < 65 years old)	0.986	0.564–1.722	0.960	1.560	0.846–2.877	0.154
Tobacco use (vs none)	1.174	0.680–2.027	0.565	1.745	0.946–3.218	0.075
No. of previous treatment lines > 3 (vs ≤ 3)	1.523	0.870–2.669	0.141	0.890	0.486–1.629	0.706
ANC	1.095	1.030–1.163	0.003*	1.057	1.003–1.113	0.037*

Notes: Cox proportional hazard models using PFS and OS as a timescale to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). *$p<0.05$.

Anlotinib is a type of antiangiogenetic therapy that plays a critical role in the alleviation of the proliferation and invasion of malignant tumor cells. In the current study, the median PFS and OS were 5.5 months (IQR, 4.0–8.0) and 9.5 months (IQR, 6.0–13.4), respectively, which were in line with the results from ALTER 0303 trial and some other retrospective studies.[9,17] Moreover, considerable improvements in the ORR (16.9%) and DCR (84.5%) were also observed in our study, which indicated that patients with advanced lung cancer could derive the clinical benefit of anlotinib in the real world.

With regard to the prognosis of lung cancer patients on anlotinib therapy, the potential predictive biomarkers are limited and insufficient. A recent retrospective study preliminarily found that tumor cavitation was an independent factor for predicting better PFS, but only a small number of patients with extensive-stage SCLC was included.[18] Another large-scale study collected data from the ALTER0303 trial and concluded that baseline characteristics such as elevated thyroid-stimulating hormone, blood glucose, triglyceride levels, and hypertension were protective factors of prognosis in refractory NSCLC patients
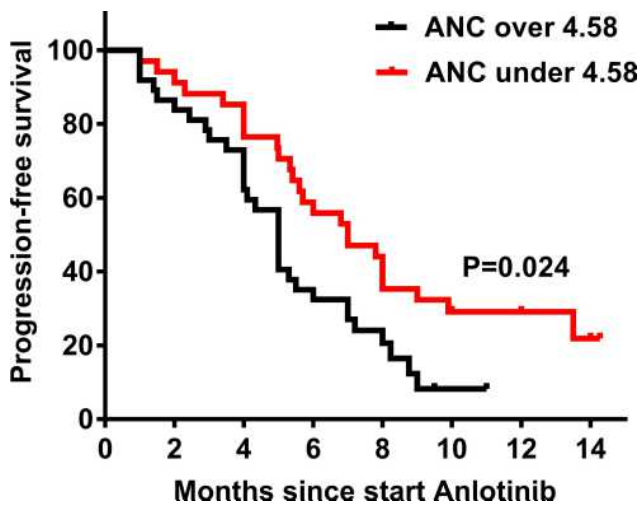
Figure 2 Progression-free survival (PFS) according to absolute neutrophil count (ANC). In the group with ANC ≥ 4.58, the median PFS (mPFS) is 7.0 months, and the 95% confidence interval (CI) is 4.4–9.6 months; In the group with ANC < 4.58, the mPFS is 5.0 months, and the 95% CI is 4.4–5.7 months. P value is 0.024.
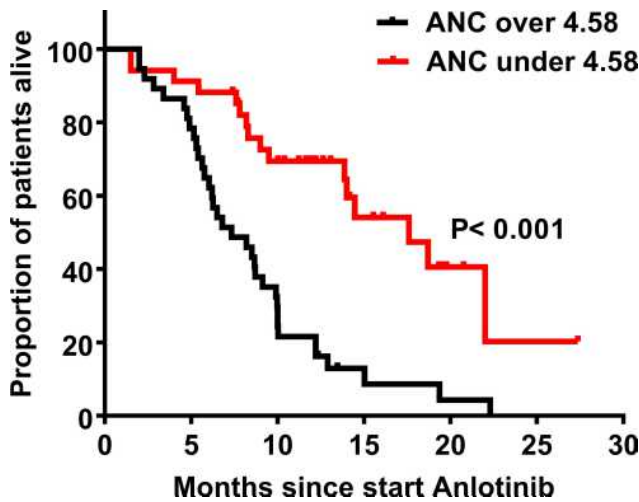

Figure 3 Overall survival (OS) according to ANC. In the group with ANC ≥ 4.58, the median OS (mOS) is 17.6 months, and the 95% CI is 12.3–22.9 months; In the group with ANC < 4.58, the mOS is 7.3 months, and the 95% CI is 4.7–10.0 months. P value is less than 0.001.

receiving anlotinib.[19] This study also showed that a high post-therapeutic peripheral blood granulocyte/lymphocyte ratio was an independent risk factor for PFS and OS, which attracted our attention.

Neutrophils are the most abundant type of innate immune cells. Accumulating evidence indicates that neutrophils play an important role in tumor proliferation, aggressiveness, and dissemination, as well as in immune suppression, through their interaction with cancer and immune cells in the blood and tumor microenvironment.[20] Moreover, ANC has always been considered as a biomarker for the prognosis of lung

Table 4 ORR, PFS and OS According to Median ANC

ANC	N for CR+PR	Percentage (%)	P value
< 4.58	9	26.5	
≥ 4.58	3	8.1	0.057
ANC	**mPFS**	**95% CI**	**P value**
< 4.58	7	4.4–9.6	
≥ 4.58	5	4.4–5.7	0.024*
ANC	**mOS**	**95% CI**	**P value**
< 4.58	17.6	12.3–22.9	
≥ 4.58	7.3	4.7–10.0	< 0.001*

Notes: The response to anlotinib between different groups were compared by Pearson χ2. The Log rank test was used for univariate analyses of PFS and OS. * $p<0.05$.

cancer patients. An analysis by the Japan Multinational Trial Organization reported that the ANC was higher in lung cancer patients than in healthy subjects, and the level of pretreatment ANC was an independent prognostic factor for advanced lung cancer.[21] Studies conducted in China and other countries have concluded that patients with abnormally increased peripheral blood granulocyte levels had a shorter tumor-free survival time after lung surgery compared to patients with normal levels. Zer et al also reported that lower ANC levels during treatment was associated with the response to PD-1 axis inhibitors.[22] One possible explanation
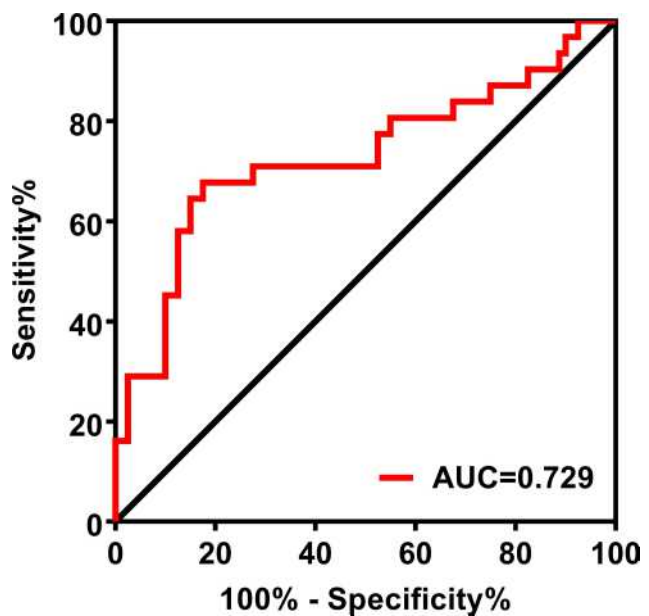

Figure 4 ROC curve of the ANC for predicting 10-month survival of patients with advanced lung cancer. The area under the curve (AUC) of the ROC curve was 0.729 The sensitivity and specificity were 82.5% and 67.7%, respectively.

is that leukocytosis caused by granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor made the lung tumors more aggressive. Another hypothesis is that the cytokines interleukin-6 and tumor necrosis factor-alpha could also induce neutrophilia, which implies suppression of anti-tumor immunity and is indicative of a poor prognosis.[21]

As for anti-VEGF/VEGFR therapy, Botta et al carried out an observational retrospective study and found that a high number of circulating neutrophils as well as a high NLR were associated with a shorter PFS and OS in patients with advanced NSCLC who received bevacizumab (anti-VEGF) treatment.[16] In patients with metastatic renal cell carcinoma, Keizman et al showed that high NLR was associated with worse efficacy of the VEGFR inhibitor (sunitinib).[23] Our study reached a similar conclusion and found that high levels of ANC were accompanied by a lower ORR, PFS and OS in lung cancer patients treated with anlotinib. In addition to the pro-invasive and immunosuppressive effects of neutrophils mentioned above, preclinical studies have also shown that inflammatory cells derived from the bone marrow such as neutrophils play a crucial role in the resistance to anti-angiogenesis therapy.[24] More neutrophils in the tumor micro-environment may promote angiogenesis by releasing different pro-angiogenic factors such as VEGF, interleukin-8 and Bv8, or proteases such as matrix metalloproteinase −9 and elastases.[25] Finally, anti-VEGF/VEGFR drugs (such as beva-cizumab and anlotinib) may not block the angiogenic switch adequately. Therefore, the therapeutic effect of anlotinib is weaken in patients with lung cancer with relatively high ANC.

Other serological indicators such as CRP and ALC, which represent the systemic inflammatory and immune status in the tumor microenvironment, were also analyzed in our study.[26] Previous studies had elucidated that CRP was inversely correlated with the presence of $CD4^+$ infiltrating lymphocytes in the tumor milieu, which in turn is associated with poor prognosis in clinical settings.[27] Additionally, a high peripheral blood neutrophils/lymphocyte ratio has been relative to be a risk factor for patient outcome.[19] Platelets have been demonstrated to be associated with angiogenesis and tumor progression, and PLR is reportedly related to poor prognosis in NSCLC patients.[28,29] None of these parameters were found to be statistically significant in our study. On one hand, it might be that the number of patients in our study was not enough to verify the phenomena; on the other hand, these parameters may only affect the prognosis of the lung tumor itself and have no effect on the therapeutic efficacy of anlotinib.

Our study has other limitations. The small number of patients in our center might not be sufficient to support the conclusion. For example, while the ORR of the high-value ANC group was 8.1% and that of the low-value group was 26.5%, the difference in ORR between the two groups was insignificant. Moreover, although we included prior treatment in the multivariate analysis model, subsequent treatment following anlotinib therapy was not evaluated. Finally, regarding the prognosis of patients treated with anlotinib, there was a lack of exploration between the inflammatory parameters and safety of anlotinib, including the adverse events.

Conclusion

In summary, patients with lower ANC in the peripheral blood are more likely to be benefit from anlotinib treatment in the real world. It is believed that the elevation of ANC in patients with poor prognosis may be related to the inflammatory response in the local tumor microenvironment. However, the specific mechanism needs to be explored further to validate the results in anticipation of contributions to clinical oncology in the future.

Ethics Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Ruijin hospital and individual consent for this retrospective analysis was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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