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Temozolomide and anlotinib as second-line therapy for non-small cell lung cancer patients with brain metastases: a retrospective cohort study

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Brain metastases (BM) are a common and challenging complication of advanced non-small cell lung cancer (NSCLC). This study aimed to evaluate the efficacy and safety of the combination of temozolomide (TMZ) and anlotinib as a second-line treatment in advanced NSCLC patients with BM. Clinical data of advanced NSCLC patients with BM between January 2020 and December 2023 were retrospectively reviewed and analyzed. All patients received TMZ combined with anlotinib as a second-line treatment. The primary endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). A total of 52 patients were enrolled, with 20 females and 32 males. The median PFS and OS were 5.0 months and 10.0 months. The ORR and DCR were 25% and 65%, respectively. Subgroup analysis demonstrated that patients who developed AEs such as hypertension, proteinuria, and hand-foot syndrome, as well as those with a favorable diagnosis-specified graded prognosis assessment score, had better efficacy outcomes, indicating these features may help to identify the priority population for this regimen. Common AEs, including hematological toxicity, fatigue, and hypertension, were generally manageable with dose adjustments and supportive care. TMZ combined with anlotinib could be a safe and effective second-line treatment option for advanced NSCLC patients with BM. Prospective trials are warranted to confirm these findings and optimize the treatment strategy.

Key words: temozolomide; anlotinib; brain metastasis; NSCLC

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and the leading cause of cancer-related mortality worldwide [1]. Over recent decades, significant advances have been made in NSCLC; however, patients with distant metastasis, especially brain metastasis (BM), still face unsatisfactory outcomes. BM occur in 25–40% of advanced NSCLC patients and significantly worsen prognosis and quality of life, with median survival ranging from 4–6 months without treatment [2].

The management of BM involves a combination of modalities, including surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and systemic therapy. However, the optimal treatment approach remains undefined, particularly for patients with progressive disease after first-line therapy [3].

Temozolomide (TMZ) is an oral alkylating agent with activity against BM in various solid tumors [4], including NSCLC, glioblastoma multiforme (GBM) [5], and melanoma [6]. However, its efficacy as monotherapy is limited, with response rates ranging from 5–10% [7].

Anlotinib is a novel multi-targeted tyrosine kinase inhibitor (TKI) that inhibits angiogenesis and tumor growth through blocking VEGFR, PDGFR, FGFR, and other kinases [8]. It has shown promising efficacy in the treatment of advanced NSCLC, both as a monotherapy and in combination therapies. Preclinical studies have suggested that anlotinib may penetrate the blood-brain barrier and exert anti-cancer function in the CNS [9].

Given the limited efficacy of single-agent TMZ and the promising feature of anlotinib, their combination may represent a rational regimen for treating advanced NSCLC with BM. This study evaluates the efficacy and safety of TMZ combined with anlotinib as a second-line therapy in this setting and explores potential predictors for treatment response.

Patients and methods

Study design. This retrospective study evaluated the efficacy and safety of TMZ combined with anlotinib as a second-line treatment in advanced NSCLC patients with BM. The patients received second-line treatment at Hubei Cancer Hospital between January 2020 to December 2023.

Ethics approval. The study complied with the principles outlined in the Declaration of Helsinki (revised in 2013). Ethical approval for this retrospective trial was obtained from the Ethics Committee of Hubei Cancer Hospital, affiliated with Tongji Medical College, Wuhan, China (Approval No. HBCHEC2020201). Informed consent was waived due to its retrospective nature.

Patient selection. Patients eligible for inclusion met the following criteria: 1) histologically documented diagnosis of NSCLC; 2) presence of BM; 3) progression after first-line treatment; 4) ECOG performance status of 0–2; 5) sufficient organ function; and 6) complete medical records. Exclusion criteria included active systemic disease, prior TMZ or anlotinib treatment, or concurrent malignancies.

Treatment protocol. TMZ was administered intravenously at a dose of 150 mg/m² every three weeks, combined with oral anlotinib at 12 mg/day for two weeks, followed by a one-week break (three-week cycle). Dose reductions of anlotinib to 10 mg or 8 mg were permitted in the event of severe AEs. Treatment continued until progression or intolerable toxicity.

Efficacy evaluation. The primary endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). OS is defined as the time from the initiation of second-line therapy to death from any cause; PFS is defined as the time from the start of treatment to disease progression or death. For patients with no available data on death or disease progression, data were censored at the last known follow-up date. BM was assessed using enhanced magnetic resonance imaging (MRI) or computed tomography (CT) scans, performed prior to and during regular follow-up visits. Tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the revised Response Assessment in Neuro-Oncology Brain Metastasis (RANO-BM) criteria.

Safety evaluation. AEs were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. hematologic and non-hematologic toxicities, including fatigue, hypertension, proteinuria, and hand-foot syndrome, were recorded and managed accordingly.

Statistical analysis. Data analysis was performed using SPSS 13.0 software. Descriptive summaries of PFS and OS were provided, along with their two-sided 95% confidence intervals (CIs). PFS and OS were estimated using the Kaplan-Meier method, and corresponding graphs were generated using Graph Prism 5.0. A p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristic. In total, 52 patients were enrolled. 20 were females and 32 were males, with an average age of 67 years. Most males were heavy smokers, while females were predominantly non-smokers. Lung adenocarcinoma was the most common histological subtype, followed by

Table 1. Baseline clinical characteristics of the study cohort.

Characteristics	No. of patients (%)
Age	
years	67
range	47–75
Gender	
male	32 (61.54%)
female	20 (38.46%)
Smoking history	
never smoker	15 (28.85%)
former smoker	37 (71.15%)
Histology	
adenocarcinoma	31 (59.62%)
squamous carcinoma	21 (40.38%)
ECOG score	
0–1	39 (75.00%)
≥2	13 (25.00%)
GPA score	
0–1	8 (15.38%)
1.5–2.0	13 (25.00%)
2.5–3.0	14 (26.92%)
3.5–4.0	17 (32.69%)
Number of metastatic lesions	
single lesion (1 lesion)	11 (21.15%)
oligometastatic disease (2–4 lesions)	15 (28.85%)
multiple metastases (5–10 lesions)	16 (30.77%)
disseminated metastases (> 10 lesions)	10 (19.23%)
PD–L1 expression level	
<1%	26 (50.00%)
1–49%	16 (30.77%)
>>50%	10 (19.23%)
Previous Radiotherapy	
yes	15 (28.85%)
no	37 (71.15%)
Brain metastasis	
measurable	13 (25.00%)
unmeasurable	39 (75.00%)
Bone metastasis	
yes	37 (71.15%)
no	15 (28.85%)
Liver metastasis	
yes	9 (17.31%)
no	43 (82.69%)
Stage	
IVA	8 (15.38%)
IVB	20 (38.46%)
IVC	24 (46.15%)

squamous cell lung carcinoma (SqcLC). Approximately 75% of the patients had measurable BM. The Eastern Cooperative Oncology Group (ECOG) performance status ranged from 0 to 2. Most patients were EGFR wild-type, with three harboring EGFR mutation post-TKI progression. In terms of the proportion of patients classified by the number of brain metastases at enrollment, the proportions of patients with single lesion (1 lesion), oligometastatic disease (2–4 lesions), multiple metastases (5–10 lesions), and disseminated metastases (>10 lesions) were 11 (21.15%), 15 (28.85%), 16 (30.77%), and 10 (19.23%), respectively. (Table 1).

Prior treatment. Most patients (EGFR wild type) had received two or more lines of chemotherapy, commonly pemetrexed plus platinum or docetaxel/gemcitabine plus platinum in the first-line therapy. 28.85% of patients underwent WBRT ≥3 months prior. EGFR-mutant patients had been treated with TKI (icotinib, erlotinib, or gefitinib). Additional testing confirmed mutations including T790M and L858R, guiding subsequent osimertinib or standard chemotherapy (Table 1).

Efficiency. As of the data cutoff date, all patients had received the combination therapy of TMZ and anlotinib for at least two cycles, with an average of three cycles. No complete responses were observed; 13 patients had a partial response, 21 patients achieved stable disease, and 18 patients progressed. DCR was 65.38% and ORR was 25.00%. Intracranial and extracranial ORR were 5% and 20%, respectively. Median PFS and OS were 5.0 months (95% CI 3.97–5.64) and 10.0 months (95% CI 7.56–10.90) (Table 2, Figures 1A, 1B). Aside from therapeutic efficacy, in terms of quality-of-life improvement, the proportion of patients whose performance status (ECOG score) improved from 1 to 0 reached 50%, and the proportion of those whose score improved from 2 to 1 was nearly 15%. As most patients experienced significant improvements in quality of life after treatment, the proportion of those requiring long-term bed rest significantly decreased. Due to side effects, only less than 10% of patients required long-term bed rest because of treatment-related toxicity.

Biomarker exploration. Subgroup analyses revealed that PD-L1 status was not associated with a difference in efficacy. Patients with PD-L1 positive (+) (≥1%) and PD-L1 negative (–) (<1%) demonstrated the same mPFS and mOS (PD-L1 positive (+) vs. PD-L1 negative (–): mPFS 5.0 months vs. 5.0 months, p=0.58, HR=1.00, 95% CI 0.42–1.58; mOS 10.0 months vs. 10.0 months, p=0.78, HR=1.00, 95% CI 0.42–1.58, (Figures 1C, 1D). However, patients who experienced AEs, such as hypertension, proteinuria, or hand-foot syndrome, generally had better treatment outcomes compared to those who did not (with sAE vs. without sAE: mPFS 6.0 months vs. 4.0 months, p<0.0001, HR=1.50, 95% CI 0.94–2.07; mOS 10.5 months vs. 9.0 months, p<0.0001, HR=1.17, 95% CI 0.60–1.73; Figures 1E, 1F). Ds-GPA score correlated with the outcome that lower ds-GPA scores predict longer PFS and OS (GPA score (0–1) vs. (1.5–2) vs. (2.5–3) vs. (3.5–4), mPFS: 6.0 months vs. 5.0 months vs. 5.0 months vs. 4.0 months, p<0.0001; mOS 10.5 months vs. 10.0 months vs. 9.0 months vs. 8.0 months, p<0.0001, Figures 1G, 1H).

Table 2. Clinical activity of anlotinib plus TMZ in advanced NSCLC with BM.

	Patient No.	Ratio
Complete response	0	0
Partial response	13	25.00% (13/52)
Stable response	21	40.38% (21/52)
Progressive disease	18	34.62% (18/52)
Objective response		25.00%
Median PFS		5.0 months
Disease control rate		65.38%
Median OS		10.0 months

Table 3. Adverse events of anlotinib plus TMZ in advanced NSCLC with BM.

	anlotinib plus TMZ [n (%)]	
Adverse Event	**Any Grade**	**Grade 3 or 4**
Hematological		
Leukopenia	18 (34.62%)	3 (5.77%)
Neutropenia	17 (32.69%)	3 (5.77%)
Anemia	10 (19.23%)	0%
Thrombocytopenia	15 (28.85%)	2 (3.85%)
Nonhematologic		
Hypertension	14 (26.92%)	3 (5.77%)
Hand-foot syndrome	16 (30.77%)	3 (5.77%)
Proteinuria	10 (19.23%)	3 (5.77%)
Elevated transaminase	8 (15.38%)	3 (5.77%)
Hyperbilirubinemia	3 (5.77%)	0%
Bleeding	0%	0%
Fatigue	18 (34.62%)	0%
ALP increased	3 (5.77%)	0%
Elevated GGT	4 (7.69%)	0%
Abdominal pain	5 (9.62%)	0%
Decreased appetite	25 (48.08%)	0%
Hypoproteinemia	4 (7.69%)	0%
Diarrhea	6 (11.54%)	0%
Elevated LDH	3 (5.77%)	0%
Oral ulcer	6 (11.54%)	0%
Stomatitis	7 (13.46%)	0%
Dysphagia	5 (9.62%)	0%
Dysphonia	4 (7.69%)	0%
Rash	3 (1.92%)	0%

Toxicity. Common AEs included neutropenia, leukopenia, thrombocytopenia, anemia, decreased appetite, fatigue, hand-foot syndrome, hypertension, and proteinuria. Most were grade 1 or 2 and well tolerated. Grade 3 or 4 occurred in less than 40% of patients, including leukopenia, thrombocytopenia, neutropenia, hand-foot syndrome, hypertension, and proteinuria. Most of the AEs can be alleviated with supportive care. Treatment discontinuation occurred in 12%. (Table 3).

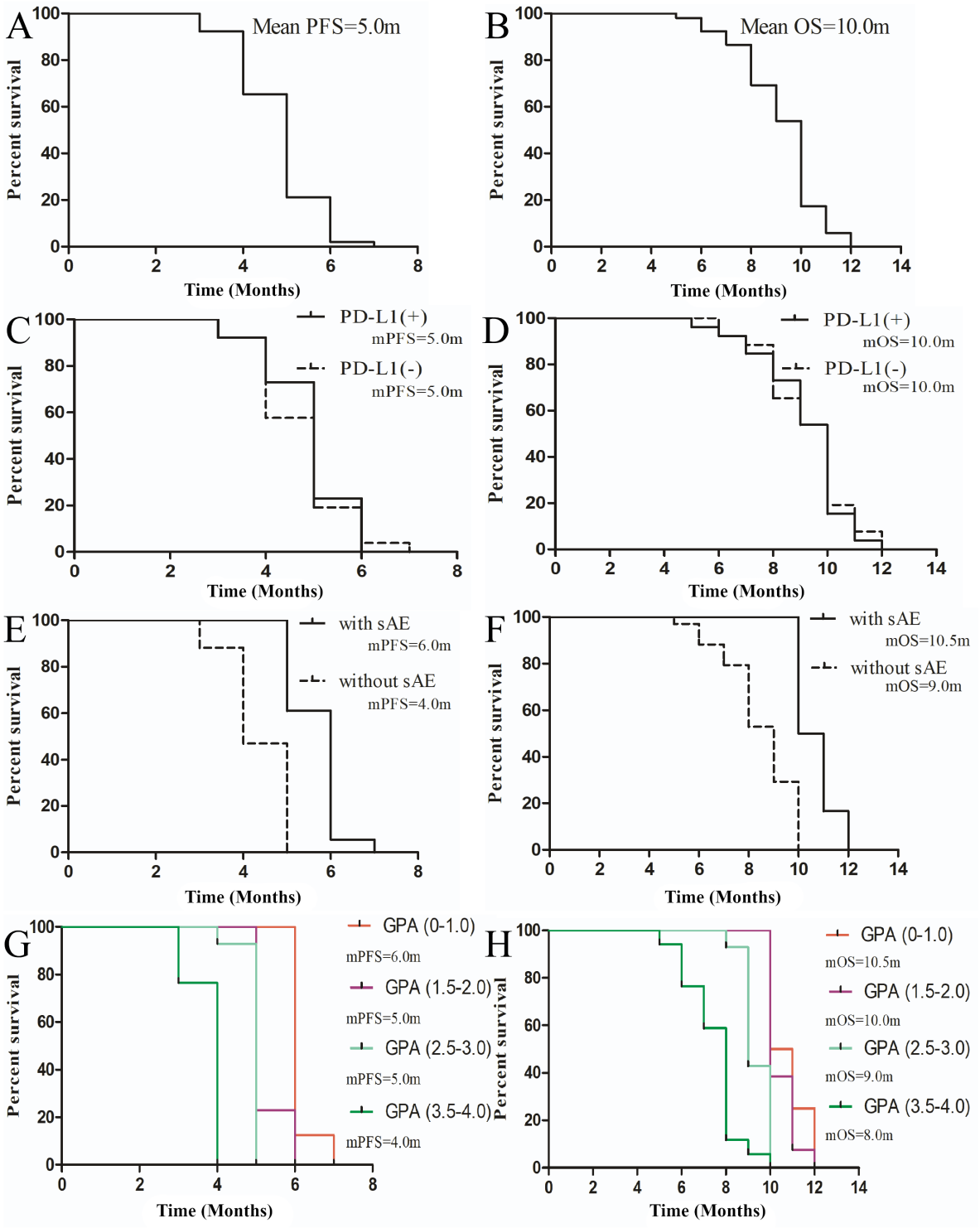

Figure 1. PFS and OS analysis of the general population and subgroup patients of advanced NSCLC with BM who accepted the drug combination of anlotinib and TMZ in this study. A, B) The overall PFS and OS in this study. C, D) Comparisons of PFS and OS between patients with different PD-L1 expression levels (PD-L1(+) vs. PD-L1(–)). E, F) Comparisons of PFS and OS between these patients with sAE and without sAE. G, H) Comparisons of PFS and OS among these patients according to the category of different dsGPA score. Abbreviations: mPFS-median progression-free survival; mOS-median overall survival; PD-L1-programmed death ligand 1; NSCLC-non-small cell lung cancer; Ds-GPA-Diagnosis-specified Graded Prognosis Assessment; Notes: PD-L1(+)-means PD-L1 ≥ 1%, while PD-L1(–) means PD-L1 (< 1%). sAE means specific Adverse Event (such as proteinuria, hypertension, or hand-foot syndrome)ç

Discussion

The treatment of advanced NSCLC with BM remains a major clinical challenge. Radiotherapy is the mainstay for BM, but it only provides short-term efficacy and is usually accompanied by comorbidities such as cognitive dysfunction [3]. Targeted therapies [10] and immune checkpoint inhibitors (ICIs) have been rapidly developed as cancer treatment modalities [10, 11]; nevertheless, their efficacy was limited in the setting of BM [12]. These limitations underscore the urgent need for further research and development in this field. Given the growing trend toward combination therapy, optimizing existing drug regimens may represent a promising strategy to improve outcomes for patients with BM [13–15].

In our study, we evidenced that the combination of TMZ and anlotinib demonstrated promising efficacy and manageable toxicity as a second-line treatment option for advanced NSCLC patients with BM.

The ORR of 25% observed in our cohort was extremely higher than that reported for monotherapy of TMZ (ORR less than 10%), or anlotinib alone (ORR of 14%), or ICIs (ORR of 9%). Furthermore, the median PFS and OS in our patients were 5.0 months and 10.0 months, which were dramatically longer than those reported for anlotinib monotherapy (PFS=4.0 months, OS=8.5 months) or ICIs (PFS=2.8 months, OS=7.5 months) [7, 9, 16]. Compared to previously reported clinical outcomes for combinations of anlotinib or TMZ with traditional treatment modalities such as radiotherapy, our results also revealed significant advantages in efficacy and safety [16–18].

Subgroup analyses revealed several clinical factors associated with treatment outcomes. Notably, patients experiencing sAE such as hypertension, proteinuria, or hand-foot syndrome demonstrated longer OS and PFS compared to those who did not [19]. This finding suggested that specific AEs may serve as potential prognostic markers. Additionally, the ds-GPA score also emerged as a significant prognostic indicator. Patients with lower ds-GPA scores presented superior OS and PFS [20]. This highlights the importance of personalized treatment strategies tailored to individual ds-GPA scores. Interestingly, contrary to previous studies indicating that PD-L1expression is positively associated with better response to immunotherapy and chemotherapy [21, 22], our findings showed no significant correlation between PD-L1 status and treatment efficacy. This discrepancy may reflect the distinct immune microenvironment features of BM [23]. Therefore, future strategies should prioritize individualized treatment planning based on stratification tools like ds-GPA. Further exploration of biomarkers and advanced imaging techniques may refine patient stratification and optimize treatment strategy [24, 25].

In terms of toxicity, the combination therapy was generally well-tolerated. The most common AEs were grade 1–2, including fatigue, hypertension, proteinuria, and hand-foot syndrome. Grade 3–4 hematological and non-hematological toxicities were infrequent and successfully managed with timely monitoring and supportive care [26–28].

As regards the potential mechanism of this combination, TMZ is known to enhance blood-brain barrier penetration, enabling anlotinib to enter the BM and exert antiangiogenic effect, thereby inhibiting tumor growth, proliferation, and metastasis [12, 29–31]. Therefore, TMZ mainly acts as a "gate opener" rather than a direct cytotoxic agent, allowing for reduced dosing without compromising the synergistic efficacy of the combination [29–35]. This regimen may improve patient tolerance and consequently enhance the quality of life.

In conclusion, the combination of TMZ and anlotinib appears to be an effective and tolerable regimen as a second-line treatment for advanced NSCLC patients with BM. Despite promising results, limitations such as retrospective nature, small sample size, and single-center design may restrict the generalizability of these findings. Future studies should focus on conducting larger-scale prospective trials to further establish the role of this combination in clinical practice [21–23].

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