

Prophylactic cerebral irradiation sensitizes relapsed sensitive small cell lung cancer to temozolomide: A retrospective cohort study

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Abstract. Prophylactic cerebral irradiation (PCI) reduces the rate of brain metastasis and improves the prognosis of patients with small cell lung cancer (SCLC), but little is known about the effect of PCI on second-line chemotherapy in patients with relapsed sensitive SCLC. This retrospective cohort study included a total of 164 patients with relapsed sensitive SCLC, 20 of whom were administered temozolomide (TMZ). Categorical clinical variables were compared between subgroups with the chi-square test or Fisher's exact test, continuous clinical variables were compared with the t-test or one-way ANOVA, and the impact on overall survival

(OS) was assessed using Kaplan-Meier analysis with the log-rank test. In general, TMZ prolonged the OS of patients with SCLC with brain metastasis from 12.0 to 19.0 months [P=0.0109, hazard ratio (HR): 0.4789, 95% CI: 0.2470-0.9287]. Furthermore, the administration of PCI improved the effects of TMZ on patients with SCLC with brain metastasis, with an increase in OS from 16.0 to 36.5 months (P=0.0017, HR: 3.634, 95% CI: 1.083-12.20); additionally, no difference was observed on the basis of the history of chemotherapy or state of brain metastasis. For the local response evaluation, the overall response rate reached 75.0% for both brain metastasis and extracranial lesions in the two-cycle evaluation, remained at 30.0 and 25.0% in the four-cycle and more-cycle evaluations, respectively, and was minimally influenced by the history of chemotherapy or PCI. In conclusion, the results of this study suggest that PCI may be valuable for patients with relapsed sensitive SCLC with brain metastasis who are receiving TMZ treatment, and it may also serve as an effective regimen to prevent local progression of extracranial lesions; however, more evidence is needed.

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Introduction

Small cell lung cancer (SCLC) is a highly aggressive cancer that accounts for ~15% of lung cancer cases (1). SCLC cells originate from neuroendocrine precursor cells (2), and SCLC cells tend to grow rapidly and metastasize in the early stage. Therefore, in most patients, late-stage SCLC has already developed by the time of diagnosis (3), and the prognosis of SCLC is poor, with a median overall survival (OS) of ~10 months (4-6). In recent decades, the first-line treatment for SCLC has been the combination of etoposide and platinum compounds (7,8). Although approximately two-thirds

of patients respond to this regimen, most patients experience relapse or progression soon after first-line treatment; hence, the prognosis remains poor (9). More recently, the novel immune checkpoint inhibitors atezolizumab and durvalumab were approved for first-line treatment in patients with late-stage SCLC. For instance, in a randomised, controlled, open-label, phase 3 trial, 34% of the 268 patients administered Durvalumab plus platinum-etoposide as the first-line therapy remained alive at 18 months, whereas only 25% of the platinum-etoposide group (269 cases) survived, with an improvement in OS provided by addition of Durvalumab [hazard ratio (HR): 0.73] (10). Similar results were also reported in another double-blinded, placebo-controlled, phase 3 trial, where 201 patients were randomly assigned to the atezolizumab group and 202 patients to the placebo group. The median OS was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (HR: 0.70) (11). However, further studies are needed to verify the new drugs and new combinations on the outcomes for patients with SCLC.

SCLC is divided into sensitive and refractory disease on the basis of the time elapsed between the first-line treatment and relapse or resistance (within or beyond 90 days). Currently, only topotecan is approved as a second-line treatment for relapsed SCLC (12), and the results of certain clinical trials have shown promise for combination chemotherapy (13,14). Temozolomide (TMZ) is an oral alkylating agent that is mainly administered to patients with glioblastoma (GBM). In 2010, Zauderer *et al* (15) reported for the first time on two patients with SCLC with leptomeningeal metastases who experienced a marked response to TMZ treatment. The results of a phase II trial proved the activity of TMZ in patients with relapsed SCLC, particularly those with brain metastases (16). A 5-day dosing regimen of TMZ was subsequently reported to be effective for patients with relapsed SCLC (17). In addition, synergy between TMZ and novel poly(ADP-ribose) polymerase-1 inhibitors, including veliparib, rucaparib and olaparib, has been demonstrated in multiple clinical trials (18-20). Currently, TMZ is incorporated into treatment guidelines for relapsed SCLC, for which the level of evidence and strength of recommendation is 2A (21). The present study focused on the influence of clinical factors on TMZ treatment, including a history of cigarette smoking and alcohol consumption, cardiovascular complications and previous radiotherapy, particularly prophylactic cerebral irradiation (PCI) treatment, and provided insights into its effect on extracranial lesions in patients with relapsed SCLC.

Patients and methods

Patients and data collection. This retrospective cohort study involved the collection of data from patients with relapsed sensitive SCLC according to their clinical records, who were treated at the 81st Group Army Hospital of the People's Liberation Army (Zhangjiakou, China) between June 2010 and December 2020; the dates refer to the period from the first encounter at the hospital to the last follow-up. The inclusion criteria were as follows: i) All patients were pathologically diagnosed with SCLC and had received inpatient radio- or chemotherapy; ii) sensitive patients were defined as

those who experienced progression or relapse ≥ 90 days after completion of first-line chemotherapy; iii) patients with brain metastasis were divided into TMZ and non-TMZ groups, where the former group was administered 75 mg/m²/d TMZ for 21 days of a 28-day cycle; iv) patients in the PCI group were prescribed 2.5 Gy irradiation, which was administered daily for 5 days per week, and a total of 30 Gy through intensity-modulated radiation therapy, no longer than one month after the first-line therapy. The dose limit for both the hippocampus and the lens was 9.0 Gy; and v) regular follow-up was carried out every month, mainly through telephone or inpatient questionnaires.

The final study population comprised 164 patients with SCLC (median age: 58.64 years, 74.4% male), with detailed characteristics summarized in Table SI. For patients in the limited stage, which refers to stages I-III (any T, any N, M0), who could be safely treated with definitive radiation doses according to the American Joint Committee on Cancer definition from 2010 (22), all were prescribed PCI. However, for those in the advanced stage, only patients evaluated as having complete response or partial response (PR) were prescribed PCI. A total of 20 patients were included in the TMZ treatment group, of which 12 received PCI. For combination with vindesine (VDS), 8 patients in the TMZ group were simultaneously administered of VDS at 3 mg/m²/week for a 28-day cycle. The clinical data collected included age at diagnosis, sex, complications of diabetes and hypertension, family history of cancer, habits of cigarette use and alcohol consumption, OS, overall response rate (ORR), previous radio/chemotherapy and the main types of side effects. The ORR was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 based on contrast-enhanced CT or MRI (23) and performed every two treatment cycles. In light of limited cases receiving >4 courses of TMZ treatment, patients were divided into three subgroups based on the courses of TMZ treatment (≤ 2 , 2-4 and >4).

Statistical analysis. GraphPad Prism 8.0 software (Dotmatics) was used to analyse the data. Nonparametric data were presented as counts and frequencies and comparisons were performed with the chi-square test or Fisher's exact test. For continuous variables, expressed as the mean \pm standard deviation, a t-test or one-way ANOVA, followed by Tukey's highly-significant differences post-hoc test was used. OS was defined as the period between the date of first primary malignancy diagnosis and the last known date of follow-up or date of death. Cumulative survival was evaluated by Kaplan-Meier analysis. Differences in survival curves between groups of patients were assessed using the log-rank (Mantel-Cox) test. The risk ratio (RR) of each variable with the corresponding 95% confidence interval (CI) was calculated with the Koopman asymptotic score. A two-tailed $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics of patients with SCLC. The clinical data of the patients with SCLC are provided in Table SI. There were no significant differences in terms of sex, mean age at the time of diagnosis, cigarette use or alcohol consumption,

Table I. Characteristics of the patients with small-cell lung cancer with brain metastasis treated with TMZ or not.

Characteristic	TMZ group (n=20)	Non-TMZ group (n=20)	P-value
Age, years	56.33±1.308	57.50±2.036	0.6290
Sex			>0.999
Female	6 (30.0)	5 (25.0)	
Male	14 (70.0)	15 (75.0)	
Cigarette consumption (longer than 30 years)	8 (40.0)	12 (60.0)	0.3431
Regular alcohol consumption (longer than 20 years)	6 (30.0)	7 (35.0)	>0.999
Diabetes mellitus	2 (10.0)	1 (5.0)	>0.999
Hypertension	1 (5.0)	1 (5.0)	>0.999
Family history of cancer	4 (20.0)	3 (15.0)	>0.999
PCI	12 (60.0)	18 (90.0)	0.3431
Thoracic radiotherapy	16 (80.0)	13 (65.0)	>0.999
Non-TMZ chemotherapy	19 (95.0)	19 (95.0)	>0.999
Targeted therapy	4 (20)	1 (5)	0.3416
Overall survival, months	25.80±2.769	16.70±2.413	0.0178
Main cause of death (brain metastasis/extracranial progress)	7/13	9/11	0.7475

Values are expressed as mean ± standard error, n or n (%). PCI, prophylactic cerebral irradiation; TMZ, temozolomide.

family history of cancer or cardiovascular complications between patients treated with or without TMZ. In addition, the proportions of patients who received surgery, thoracic radiotherapy, prophylactic cerebral irradiation and targeted therapy were similar between the two groups. TMZ treatment did not increase OS, which may be explained by the different proportions of patients with brain metastasis among the patients with SCLC [18.89% (20/144) for those without TMZ treatment and 100% for those in the TMZ group, $P < 0.001$; Table SI]. Therefore, OS, risk factors and the main cause of death were compared among patients with brain metastasis who were or were not treated with TMZ (the TMZ or non-TMZ group). Although there were no significant differences in the potential risk factors (Table I), the OS time of the TMZ group was significantly longer than that of the non-TMZ group. Thus, the results of the present study proved the benefits of TMZ for patients with SCLC with brain metastasis.

Factors influencing OS in patients with SCLC treated with TMZ. The effect of TMZ on the survival of patients with SCLC with brain metastasis was evaluated by Kaplan-Meier analysis, and it was observed that the median survival time in the non-TMZ group was only 12.0 months, whereas it was significantly increased to 19.0 months in the TMZ group [$P = 0.0109$, hazard ratio (HR): 0.4789, 95% CI: 0.2470-0.9287; Fig. 1A]. In addition, the OS of the two groups remained identical regardless of the number of brain metastases (Fig. 1B) and early chemotherapy regimens (Fig. 1C). Furthermore, the median survival time of patients who received PCI was 2.28-fold greater than that of patients without PCI treatment ($P = 0.0017$, HR: 0.07673, 95% CI: 0.01857-0.3171; Fig. 1D). Next, the dose-dependent effects of TMZ on OS were analysed. Although the difference was not significant, the median survival time of those who underwent >4 cycles of TMZ treatment was 36.0 months, whereas

patients who received 2 or 1 cycles of TMZ treatment had a median survival time of only 17.0 months ($P = 0.5271$, HR: 1.306, 95% CI: 0.5363-3.181; Fig. 2A). In addition, during this study, 8 patients in the TMZ group were simultaneously administered VDS (3 mg/m²/week for a 28-day cycle), but there was no difference in OS between those receiving TMZ plus VDS treatment and those receiving TMZ-only treatment ($P = 0.5029$, HR: 0.9582, 95% CI: 0.3931-2.336; Fig. 2B). Together, these results indicate that the administration of PCI but not chemotherapy regimens or the state of brain metastasis affects the prognosis of patients with SCLC with brain metastasis after TMZ treatment and that there are potential dose-dependent effects of TMZ treatment.

Effects of TMZ on the ORR of patients with SCLC. To evaluate the ORR of TMZ treatment, both brain and extracranial metastatic lesions were evaluated through CT or MRI images. As shown in Table II, 7 patients received four courses of TMZ and 4 of these patients had the opportunity to receive more courses. On the basis of the Response Evaluation Criteria in Solid Tumors, the state of stable disease (SD) and partial response (PR) was considered responsive to TMZ treatment (with no complete response observed in this study). The ORRs for brain metastasis were 75.0, 30.0 and 15% in the 2-cycle, 4-cycle and >4-cycle evaluations, respectively. The ORRs for lesions with extracranial metastasis were 75.0, 25.0 and 20%, respectively (Table II). In addition, the RR of the combination of VDS with 2-cycle TMZ treatment was 1.500 (95% CI: 0.6803-3.6893) and 1.125 (95% CI: 0.4039-3.108) for the brain and extracranial metastatic lesions, respectively. Administration of PCI before TMZ showed a limited influence on the ORRs, with a RR of 1.061 (95% CI: 0.4961-2.949) and 1.250 (95% CI: 0.4516-4.627) for brain and extracranial metastatic lesions, respectively. Similar

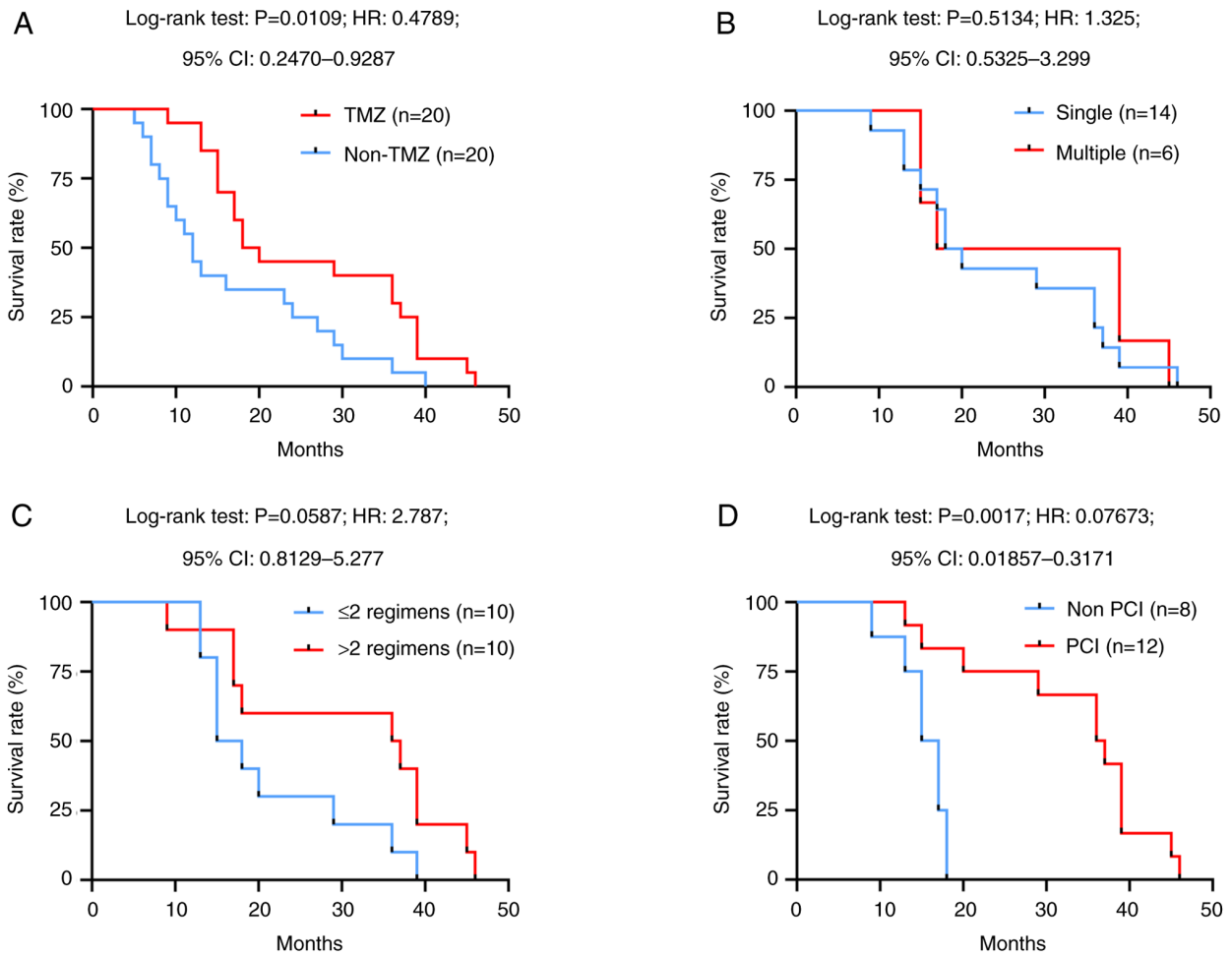


Figure 1. Factors influencing TMZ treatment in patients with SCLC with brain metastasis. (A) Kaplan-Meier curves showing the impact of TMZ treatment on the OS of patients with SCLC with brain metastasis. (B) Influence of the number of metastases on OS with TMZ treatment. (C) Influence of early chemotherapy regimens on OS with TMZ treatment. (D) Influence of PCI on OS with TMZ treatment. TMZ, temozolomide; SCLC, small-cell lung cancer; PCI, prophylactic cerebral irradiation; OS, overall survival.

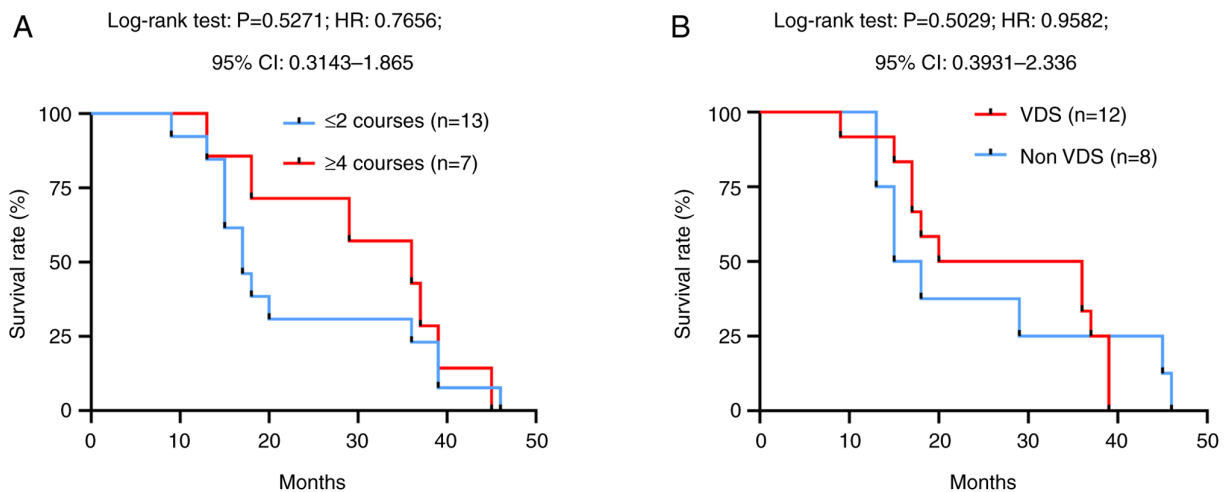


Figure 2. Effects of dosage and the combination of VDS and TMZ on TMZ treatment. Kaplan-Meier curves showing (A) the impact of the courses of TMZ treatment on the OS of patients with small-cell lung cancer with brain metastasis and (B) the influence of the combination of VDS on OS with TMZ treatment. TMZ, temozolomide; VDS, vindesine; OS, overall survival.

results were observed for different chemotherapy regimens before TMZ. Although there were no significant differences in the ORRs, >15% patients retained non-progressive disease

after two courses of TMZ treatment. Furthermore, the initial treatment regimens and medication duration did not affect the effectiveness of TMZ.

Table II. Overall response rate of brain and extracranial lesions of metastasis for TMZ.

Treatment/response	TMZ courses, n (patients)		
A, Brain metastasis			
Total (n=20)	2 (n=20)	4 (n=7)	>4 (n=4)
SD	10	5	2
PR	5	1	1
PD	1	2	1
ORR, %	75.0	30.0	15.0
Adjuvant			
No (n=8)	2 (n=8)	4 (n=4)	>4 (n=1)
SD	6	2	0
PR	2	0	0
PD	0	2	1
ORR, %	100	25.0	0
Yes (n=12)	2 (n=12)	4 (n=4)	>4 (n=3)
SD	4	3	2
PR	3	1	1
PD	1	0	0
ORR, %	58.3	33.3	25.0
RR (95% CI); P-value	1.500 (0.6803-3.6893); NS	0.6467 (0.1844-2.084); NS	/
PCI			
Yes (n=12)	2 (n=12)	4 (n=5)	>4 (n=4)
SD	7	4	2
PR	3	0	1
PD	1	1	1
ORR, %	83.3	33.3	25.0
No (n=8)	2 (n=5)	4 (n=3)	>4 (n=0)
SD	3	1	0
PR	2	1	0
PD	0	1	0
ORR, %	62.5	25.0	0
RR (95% CI); P-value	1.0610 (0.4961-2.949); NS	2.4000 (0.6897-13.41); NS	/
Number of regimens			
≤2 (n=10)	2 (n=10)	4 (n=3)	>4 (n=1)
SD	6	2	0
PR	2	0	1
PD	1	2	0
ORR, %	80.0	20.0	0
≥3 (n=10)	2 (n=10)	4 (n=4)	>4 (n=3)
SD	4	3	2
PR	3	1	0
PD	0	0	1
ORR, %	70.0	40.0	20.0
RR (95% CI); P-value	1.670 (0.5312-2.877); NS	0.6667 (1.866-2.084); NS	/
B, Extracranial metastasis			
Treatment/response			
TMZ courses, n (patients)			
Total (n=20)	2 (n=20)	4 (n=7)	>4 (n=4)
SD	8	4	1
PR	7	1	3
PD	2	2	0
ORR, %	75.0	25.0	20.0

Table II. Continued.

B, Extracranial metastasis			
Treatment/response	TMZ courses, n (patients)		
Adjuvant			
No (n=8)	2 (n=8)	4 (n=3)	>4 (n=1)
SD	4	1	1
PR	4	1	0
PD	0	1	0
ORR, %	100	25.0	12.5
Yes (n=12)	2 (n=12)	4 (n=4)	>4 (n=3)
SD	4	3	0
PR	3	0	2
PD	2	1	0
ORR, %	58.3	25.0	16.7
RR (95% CI); P-value	1.125 (0.4039-3.108); NS	0.6467 (0.1844-2.084); NS	/
PCI			
Yes (n=12)	2 (n=12)	4 (n=11)	>4 (n=4)
SD	6	4	1
PR	4	6	3
PD	2	1	0
ORR, %	83.3	83.3	33.3
No (n=8)	2 (n=5)	4 (n=3)	>4 (n=0)
SD	2	0	0
PR	3	1	0
PD	0	1	0
ORR, %	62.5	12.5	0
RR (95% CI); P-value	1.250 (0.4516-4.627); NS	(0.9803-2.684); NS	/
Number of regimens			
≤2 (n=10)	2 (n=10)	4 (n=3)	>4 (n=1)
SD	5	1	0
PR	3	1	1
PD	1	1	0
ORR, %	80.0	20.0	10.0
≥3 (n=10)	2 (n=10)	4 (n=4)	>4 (n=3)
SD	3	3	1
PR	4	0	2
PD	1	1	0
ORR, %	70.0	30.0	30.0
RR (95% CI); P-value	1.4810 (0.5407-4.511); NS	0.4444 (0.07810-1.770); NS	/

SD, stable disease; PR, partial response; PD, progressive disease; PCI, prophylactic cerebral irradiation; TMZ, temozolomide; NS, no significance; RR, risk ratio for Yes vs. No group in each category. Regimens of SCLC included the first-line therapy (Etoposide + Carboplatin or Irinotecan + Cisplatin), the second-line therapy (Topotecan, Irinotecan, Cyclophosphamide + Doxorubicin + Vincristine) and the Personalized third-line or multi-line treatment regimens and here the number represents the total regimens received.

Adverse effects of TMZ treatment in patients with SCLC. In the present study, 13 patients failed to receive 4 cycles of TMZ treatment, of whom only one experienced progression of brain metastasis, and the other 12 patients discontinued TMZ treatment because of metastasis to the liver, lymph nodes or splanchnocoel. However, the risk of severe anaemia or fatigue, the two most common adverse effects, was not elevated in this study. Additionally, only slight side effects associated with

the digestive system were observed (Table III). These results revealed that TMZ treatment was a safe second-line strategy against SCLC.

Discussion

In recent decades, the combination of TMZ or whole-brain irradiation with or without stereotactic radiotherapy has

Table III. Adverse effects of TMZ treatment.

Toxicity	TMZ group (n=20)				Non-TMZ group (n=20)				P-value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
Anemia	2 (10)	4 (20)	3 (15)	1 (5)	4 (20)	4 (20)	3 (15)	0 (0)	>0.999
Fatigue	8 (40)	6 (30)	4 (25)	0 (0)	6 (30)	7 (35)	5 (25)	0 (0)	>0.999
Vomiting	6 (30)	6 (30)	0 (0)	0 (0)	8 (40)	5 (25)	0 (0)	0 (0)	NA
Anorexia	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	NA

Values are expressed as n (%). The difference in the total number of grade 3 and grade 4 patients was compared between the two groups. TMZ, temozolomide; NA, information not available.

been considered a beneficial option for patients with GBM and non-SCLC (24,25). However, the effect of PCI in adjuvant TMZ treatment for patients with SCLC has remained underexplored. Recently, a case study reported that permanent radioactive iodine-125 seed implantation combined with TMZ metronomic chemotherapy triggered an abscopal effect and provided good local control of liver metastases in patients with SCLC (26). Thus, radiotherapy may sensitize patients with SCLC to TMZ. In addition, TMZ, as a third-line therapy, has been reported to result in a partial response in patients with pulmonary large-cell neuroendocrine carcinoma, with no severe side effects (27), which suggests TMZ is effective for treating pulmonary neuroendocrine lesions, including SCLC.

To investigate the effect of TMZ in patients with sensitive relapsed SCLC and the related risk factors, the present retrospective cohort study was performed. In accordance with a previous study (16), a significant improvement in OS was observed in the TMZ group. The present results are the first to show an underlying relationship between PCI and the effects of TMZ treatment in patients with sensitive relapsed SCLC with brain metastasis, to the best of our knowledge. In addition, although vinorelbine alone (28) or in combination with other agents (29,30) has been reported to exert toxic effects on patients with SCLC in clinical trials, no synergy between vindesine and TMZ was found in the cohort of the present study. Interestingly, in addition to a dramatic response of brain metastases to TMZ, a relatively high response rate was observed in extracranial lesions even in the four-cycle assessment. Therefore, the results of the present study support the beneficial effects of TMZ in patients with SCLC.

TMZ is an oral DNA alkylating agent that is known to cause cell cycle arrest (31), apoptosis (32) and autophagy (33,34). Because of its ability to cross the blood-brain barrier, TMZ is highly recommended as a first-line chemotherapy for astrocytoma and GBM (35,36). Through the methylation of DNA adenine and guanine residues, TMZ treatment leads to the formation of O⁶-methylguanine, N³-methyladenine and N⁷-methylguanine, which exert cytotoxic effects (37). In addition, methylated DNA can be repaired by base excision or DNA mismatch repair pathways, and mutation of related genes results in TMZ resistance (38). To date, mutations in TP53 (39), MGMT (40,41), APEX1 (42), STAT3 (43), BCRP1 (44) and other genes have been reported to result in TMZ resistance in patients with GBM. However, the state of these genes

in populations of patients with SCLC has been poorly investigated. In the present study, the gene mutation data of 249 patients with SCLC and 520 patients with GBM available from the cBioPortal website (<http://www.cbioportal.org/>) were compared. In accordance with a previous study (45), TP53 and RB1 are the most commonly mutated genes in patients with SCLC, and of note, TP53 and TTN are among the top five commonly mutated genes in both patients with SCLC and GBM. However, the resistance-related genes discussed above all exhibited relatively low mutation rates in patients with these two kinds of cancer (Table SII). Although mutation of TP53 has been proven to affect the sensitivity of GBM cells to TMZ in certain studies (37,46), the results remain controversial. Hence, mutation of the TP53 gene is not considered the primary indicator of resistance to TMZ. Therefore, in terms of gene mutations, patients with SCLC may also benefit from TMZ treatment.

TMZ has a favourable side effect profile; the most common adverse reactions are mild, e.g., myelosuppression (anaemia and fatigue) and gastrointestinal side effects (vomiting and anorexia). However, TMZ has also been reported to induce severe skin reactions (47), aplastic anaemia (48) and organizing pneumonitis (49). The occurrence and severity of side effects limit the use of TMZ in clinical applications. The dose and treatment course of TMZ, or its combination with other medications, are key factors in the occurrence of side effects. For instance, high-dose or long-term use may lead to serious side effects such as neutropenia or thrombocytopenia. The combined use of TMZ with radiotherapy may exacerbate myelosuppression or skin reactions (50). However, no significant difference in the incidence of side effects was observed between the PCI and non-PCI groups of the present study, which may be a result of separate administration of PCI and TMZ. In addition, a patient's genetic background and health status determine the severity of the side effects. Patients with an unmethylated MGMT promoter may be more resistant to TMZ and require a higher dose (51). Elderly patients or patients with impaired liver and kidney function have decreased drug metabolism ability, which may lead to drug accumulation and increased risk of toxicity (52). In the present study, no difference was observed in age, sex, smoking, alcohol consumption, diabetes mellitus, hypertension or medications between the TMZ and non-TMZ groups. Therefore, the similar incidence of side effects confirmed the safety of TMZ.

Since the present study was a single-centre study with a limited number of patients, adjusting for the influence of confounding factors through stratified analysis was impossible. For instance, it was not possible to divide the TMZ group into patients who received chemotherapy alone, radiotherapy alone or both chemotherapy and radiotherapy. For the same reason, only the role of adjuvant VDS treatment in combination with TMZ was investigated. In addition, as it was a retrospective study, selection bias was inevitable. The included patients were mostly low- and middle-income patients who underwent mainly primary examinations and chemotherapy and/or radiotherapy. Therefore, the roles of genetic testing and immunotherapy in SCLC were not investigated. A larger sample size including patients from multiple centres is necessary to determine the effect of PCI on the sensitivity of patients with SCLC to TMZ and other related risk factors.

In conclusion, because of its convenience and safety, TMZ may be an alternative treatment for patients with SCLC who have no access to hospitals (53), such as when hospital access was limited due to the COVID-19 pandemic, to control lesions within or outside of the brain.

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Availability of data and materials

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

Authors' contributions

FG, SL, SZ and DH conceived and designed the study, developed the protocol, defined inclusion criteria and obtained ethical approval. SW, YG, ZH and FL recruited patients, administered TMZ/VDS treatments and monitored adverse events. YG, ZH and FJ coordinated TMZ acquisition, validated dosing protocols and supervised data integrity. WL, RL, LL, FJ, ZH and CM collected clinical records and imaging data and performed statistical analyses. FG and FJ performed the literature review. FG, LL, SW, FJ and FL drafted the initial manuscript. SZ and FJ revised the manuscript. All authors have read and approved the final manuscript. FG and SZ independently verified the authenticity of the raw data.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of PLA 81st Group Army Hospital (Zhangjiakou,

China; approval no. JTJYY-202501). Written informed consent was obtained from all individual participants involved in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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