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ORIGINAL ARTICLE

Effectiveness of temozolomide combined with whole brain radiotherapy for non-small cell lung cancer brain metastases

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Keywords
Brain metastases; non-small-cell lung cancer; temozolomidewhole brain radiotherapy.

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Abstract

Background: We performed a retrospective analysis to compare the efficacy of whole brain radiotherapy (WBRT) combined with temozolomide (TMZ) versus WBRT alone as first-line treatment for brain metastases (BM).

Methods: Seventy-eight non-small cell lung cancer patients with BM were observed, including 45 patients who received WBRT plus TMZ (TMZ + WBRT) and 33 patients who received WBRT alone (WBRT). The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and adverse events.

Results: The TMZ + WBRT arm achieved significant improvement in ORR (P = 0.0108) compared to the WBRT arm. PFS in the TMZ + WBRT arm was significantly longer than in the RT arm (6.0 vs. 3.5 months; P = 0.038). OS was not significantly different between the two arms. Although increased adverse reactions were experienced in the TMZ + WBRT arm, patients were tolerant of the side effects. Statistically significant differences in neurocognitive function and quality of life were observed between the arms at six months.

Conclusion: Concomitant TMZ + WBRT compared to WBRT alone significantly increases ORR and median PFS in patients with BM, but no remarkable difference in median OS was found. Adding TMZ to the treatment strategy could prevent neurocognitive function and quality of life from deteriorating. Although the addition of TMZ increases the incidence of adverse effects, no significant difference was observed. Thus, TMZ is safe and effective.

Introduction

Brain metastasis (BM) is a major cause of morbidity and mortality in cancer patients and is the most common type of intracranial tumor, occurring in approximately 10–30% of adult patients with cancer.[1] BM is also a major cause of non-small cell lung cancer (NSCLC) and breast cancer death. The rate of BM in NSCLC is 30–40%. Quality of life (QoL) in patients with BM is diminished and prognosis is poor. The median overall survival (OS) of untreated patients is < 3–6 months. As a result of improvements in imaging and localization techniques, surgery or localized radiosurgery have become accepted therapeutic options for patients with a single brain lesion. However, for patients with > 3 BMs, multiple studies show that whole-brain radiotherapy (WBRT) combined with stereotactic radiotherapy does not improve survival.[2,3] Indications for surgery are limited to the main pathological diagnosis and removal of life-threatening disease. Thus, a number of studies now focus on the utilization of chemotherapy.

Chemotherapy is considered the mainstay of treatment of disseminated NSCLC, but it remains controversial as a treatment for patients with BM. Because of the existence of the blood-brain barrier (BBB), many effective chemotherapies are restricted to the central nervous system (CNS). However, some scholars have confirmed that BM can

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destroy the integrity of the BBB. In recent years, several new chemotherapies have been successfully developed to pass through the BBB, including paclitaxel, gemcitabine, Changchun Rubin, gefitinib, and temozolomide (TMZ).

TMZ is easy to administer and is well tolerated; thus, an increasing number studies have focused on its effect on BM. TMZ is a new, oral alkylating agent that has demonstrated preclinical activity against a variety of solid tumors.[4] It is an active drug for the treatment of patients with high-grade gliomas[5] and melanomas[6] and is highly bioavailable after oral administration.[7] It crosses the BBB,[8] achieving effective concentrations in the CNS, and resulting in mild adverse events.[9] Adding TMZ to WBRT may improve the response rate in NSCLC patients with BM.[10–12] The primary dose-limiting toxicity is myelosuppression, and the incidence of grade 3/4 neutropenia and thrombocytopenia is generally > 10%.[5,6,13–16] However, unlike many other alkylating agents, this myelosuppression is reversible and noncumulative.[17] A previous study indicated that WBRT combined with a low dose of TMZ (75 mg /m^2) for BM could significantly improve the objective response rate (ORR) and be fully tolerated. QoL and preservation of neurocognitive function (NCF) are the main objectives when treating patients with BM; however, the potential neurocognitive risks and influence on QoL with combined treatment of TMZ + WBRT have not been fully investigated. Thus, we investigated the survival benefits, safety, tolerability, NCF, and QoL associated with WBRT with or without TMZ for the treatment of NSCLC patients with BM.

Methods

Patient selection

We retrospectively reviewed the data of NSCLC patients with BM treated at the Shandong Cancer Hospital, affiliated with Shandong University, from January 2012 to December 2014. Eligibility criteria included a diagnosis of NSCLC and BM > 3; confirmed by magnetic resonance imaging; no history of tyrosine kinase inhibitor administration; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; a life expectancy of ≥ 3 months; good hematological (absolute neutrophil count >1500/mm^3, platelet count >100 000/mm^3) and hepatic function (total bilirubinemia < 1.25 × upper limit of normal [ULN], 2.5 × ULN in cases of liver metastases); aspartate amino transferase (AST) and alanine amino transferase (ALT) < 2 × ULN (3 × ULN in case of liver metastases); and good renal function (serum creatinine <110 μmol/L). Patients were required to have fully recovered from previous chemotherapy or local irradiation for extra-cranial disease before a prescription of 2 Gy/fraction × 20 fractions of WBRT was administered.

Patients were excluded for the following reasons: small cell or mixed small cell histology; *EGFR* mutations; < 3 weeks from the last chemotherapy; prior treatment for BM; severe inter-current medical illness or symptomatic heart diseases; prior WBRT; or use of TMZ or other targeted drugs. This study was approved by the institutional review board (20171204) and was performed at the Shandong Cancer Hospital, affiliated with Shandong University. Written informed consent was obtained from each patient before treatment.

Treatment plans

Planned conventional WBRT was administered at a daily dose of 2 Gy × 5 days each week for four weeks, for a total dose of 40 Gy. TMZ was administered orally at a dosage of 75 mg/m^2/day during WBRT and 150 mg/m^2/day × 5 days every 28 days after WBRT to fasting patients for a maximum of six additional cycles. Treatment was continued until disease progression or unacceptable toxicity. All patients received corticosteroids at the lowest dose necessary to maintain neurologic stability before and during WBRT. The corticosteroids were tapered slowly and discontinued whenever possible in the weeks after treatment. Anticonvulsants were administered when indicated. Over the course of treatment, patients with intracranial progress or new organ metastasis were not included in the study follow-up.

Patient evaluation

Baseline evaluation included a complete medical history, physical examination, determination of World Health Organization (WHO) PS, biologic evaluation, chest X-ray, chest computed tomography (CT) scan, bronchial endoscopy, abdominal ultrasound or CT scan, and bone scintigraphy. Blood counts were assessed weekly during therapy. Liver function, renal function, and electrolytes were monitored before each cycle. All patients underwent weekly neurologic examinations during treatment and a complete clinical evaluation after WBRT. When necessary, brain magnetic resonance imaging (in accordance with the baseline imaging technique), chest CT scans, and other exams were repeated every two cycles and every two months after the sixth cycle. Patient responses were evaluated according to WHO/ECOG criteria: a complete response (CR) was defined as the disappearance of all known BM; a partial response (PR), as a ≥ 50% decrease in measurable brain lesions or an objective improvement in evaluable brain lesions; stable disease (SD) referred to no change in brain lesions (< 50% decrease or < 25% increase in the size of measurable lesions); and progressive disease (PD) was

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defined as a > 25% increase in the size of some or all brain lesions and/or the appearance of any new brain lesions.

Symptoms and toxicities were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Neurocognitive and quality of life (QoL) instruments

The neuropsychological test batteries (NPTB) employed for this trial included: the Hopkins Verbal Learning Test (HVLT) for memory (both immediate and delayed recall and recognition); the Controlled Oral Word Association Test (COWAT) for language/verbal fluency; the Trail Making Test Part A (TMT-Part A) for visual and spatial scanning, attention, sequencing, and speed; and the Trail Making Test Part B (TMT-Part B) for executive/frontal lobe skills.

Quality of life was assessed using the Functional Assessment of Cancer Treatment-Lung (FACT-L) Chinese version 4.0 questionnaire, which includes 34 items on a five-point Likert scale.[18] The FACT-L has been shown to be a reliable and valid instrument to measure QoL in Chinese lung cancer patients.[19] These instruments were collected at baseline and 3, 6, and 12 months for the first year post-treatment, and then annually for 3 years. They were also collected at disease progression or relapse and at death.

Table 1 Patient demographics and baseline disease characteristics

Characteristics	Total (%)	TMZ + WBRT (%)	WBRT (%)
All patients	78 (100)	45 (100)	33 (100)
Gender			
Male	43 (55.2)	25 (55.6)	18 (54.5)
Female	35 (44.8)	20 (54.4)	15 (45.5)
Smoking			
Never	40 (51.2)	24 (53.3)	16 (48.5)
Current/former	38 (48.8)	21 (46.7)	17 (51.5)
Age			
≤ 61	29 (37.1)	15 (33.3)	14 (42.4)
> 61	49 (62.9)	30 (66.7)	19 (57.6)
Histology			
Adenocarcinoma	70 (89.7)	41 (91.1)	29 (87.9)
Non-adenocarcinoma	8 (10.3)	4 (8.9)	4 (12.1)
ECOG PS			
0	23 (29.5)	14 (31.1)	13 (39.3)
1	41 (52.6)	24 (30.8)	14 (42.2)
2	14 (17.9)	7 (38.1)	6 (18.5)
Prior chemotherapy			
No	30 (38.4)	19 (42.2)	11 (33.3)
Yes	58 (61.6)	36 (57.8)	22 (66.7)
Extracranial metastases			
No	35 (44.9)	21 (46.7)	14 (42.4)
Yes	43 (55.1)	24 (53.3)	19 (57.6)
Neurologic function evaluation			
Level I	19 (24.3)	11 (24.4)	8 (24.2)
Level II	41 (52.6)	24 (53.3)	17 (51.5)
Level III	18 (23.1)	10 (22.3)	8 (24.3)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; TMZ, temozolomide; WBRT, whole brain radiotherapy.

Statistical methods

Pearson's chi-square or Fisher's exact tests (when there were < 5 expected counts in the contingency table), were used to compare the baseline characteristics between the TMZ + WBRT and WBRT arms. OS and progression-free survival (PFS) were estimated according to the Kaplan–Meier method. OS was defined as the interval from initiation of WBRT to the date of death resulting from NSCLC. PFS was also calculated from the initiation of WBRT and the date of confirmed progression or death from any cause. If the complete survival data of a patient was not available or the disease did not progress, patient status was assumed at the last known survival and/or contact date. The baseline neurocognitive status was recorded at the first neurocognitive assessment before the start of BM treatment. $P < 0.05$ was regarded as statistically significant in two-tailed tests. SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patient characteristics

The data of 95 NSCLC patients with BM treated in our cancer center with TMZ + WBRT from January 2012 to December 2014 were retrospectively reviewed. Four patients refused treatment, two patients ceased treatment because of external BM (liver) progression, and one patient was lost to follow-up for a month after WBRT. Ten patients were excluded because they had been administered EGFR-tyrosine kinase inhibitor therapy. Consequently, 78 patients completed the experiment and their data was statistically analyzed. Forty-five (57.7%) and 33 patients (42.3%) were categorized into the TMZ + WBRT and WBRT arms, respectively (35 women and 43 men). The median age was 61 years (range 46–82), and PS was 0 or 1 in 82% of patients. Lung adenocarcinoma was the major type of cancer at 90%, with other types accounting for the remaining 10%. Fifty-eight patients had received prior chemotherapy. In addition to BM, 43% of patients had metastases in other organs. The majority of patients in both treatment groups had level I or II NCF at baseline. The baseline patient characteristics were well balanced between the two arms. Patient demographics and baseline disease characteristics are listed in Table 1.

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Response of brain lesions to treatment

As shown in Table 2, 78 patients were included in the final analysis. An objective response of BM was observed in 78 patients: 13 CR and 28 PR (91.1%) in the TMZ + WBRT arm, and 7 CRs and 15 PRs (66.7%) in the WBRT arm. The objective response in the TMZ + WBRT arm ($P = 0.008$) was significantly superior to that of the WBRT arm. SD of BM was observed in 4 (8.9%) TMZ + WBRT patients and 8 (24.2%) WBRT patients. There were three cases of PD in the WBRT arm. All responses were evaluated two months after the completion of radiation treatment and confirmed a month later.

Survival analyses

Concomitant TMZ + WBRT treatment was associated with a 58% improvement in PFS compared to WBRT alone. The median PFS of the TMZ + WBRT arm was significantly longer than that of the WBRT arm (6.0 vs. 3.5 months; $P = 0.038$) (Fig 1).

The OS was 10 months in the TMZ + WBRT arm and 7.5 months in the WBRT arm. Although the median OS of the TMZ + WBRT arm was slightly higher than in the WBRT arm (Fig 2), this difference was not statistically significant.

Adverse effects

Toxicity in the patient cohort according to CTCAE version 3.0 is listed in Table 3. The addition of TMZ to WBRT was generally well tolerated. The most frequent hematologic side effects were thrombocytopenia (51%), neutropenia (36%), and anemia (27%). Severe hematological toxicity occurred in six TMZ + WBRT patients and one WBRT patient. Of the 45 patients administered TMZ + WBRT, 7 (16%) developed severe thrombocytopenia, and 3 developed severe leukocytopenia. The non-hematological toxicities were mainly mild; the most common non-hematologic toxicities were headache (67%), nausea (60%), and fatigue (56%). Most toxicities were well controlled by supportive care. Hepatic, renal, cardiac, or severe neurological toxicity were not observed in our series. Overall, all toxicities were generally brief, reversible, and manageable.

Table 2 Brain lesion response to treatment

Parameter	TMZ + WBRT ($n = 45$) (%)	WBRT ($n = 33$) (%)	*P*
CR	13 (28.9)	7 (21.2)	
PR	28 (62.2)	15 (45.5)	
Objective response (CR+ PR)	41 (91.1)	22 (66.7)	0.008
Stable disease	4 (8.9)	8 (24.2)	
Progressive disease	–	3 (9.1)	

CR, complete response; PR, partial response; RT, radiotherapy; TMZ, temozolomide; WBRT, whole brain radiotherapy.

Impact of TMZ + WBRT on QoL

As shown in Table 4, all patients who answered the questionnaire at baseline were included in the evaluation. Seventy-eight (100%) patients completed baseline questionnaires over the first nine months of follow-up. There was no significant difference in compliance between the two arms ($P > 0.05$). Table 5 shows the deterioration at nine months through a reliable change index threshold baseline. There was no significant difference between NCF and QoL scores in the two groups before treatment ($P > 0.05$). Of the 42 patients assessed in the TMZ + WBRT arm, 8 showed deterioration in the HVLT with delayed recall, but this result was not significantly lower than in the WBRT arm ($P = 0.91$), in which 6 out of 31 patients had delayed recall. No statistically significant differences were observed in the TMT ($P = 0.40$), COWAT ($P = 0.64$), or FACT-G ($P = 0.97$) at three months. However, there was significantly greater deterioration in HVLT total recall ($P = 0.026$), TMT delayed recall ($P = 0.035$), COWAT ($P = 0.039$), and FACT-G ($P = 0.037$) in the WBRT compared to the TMZ + WBRT arm at six months. No statistically significant differences between the two arms were observed at nine months ($P > 0$ 0.05).

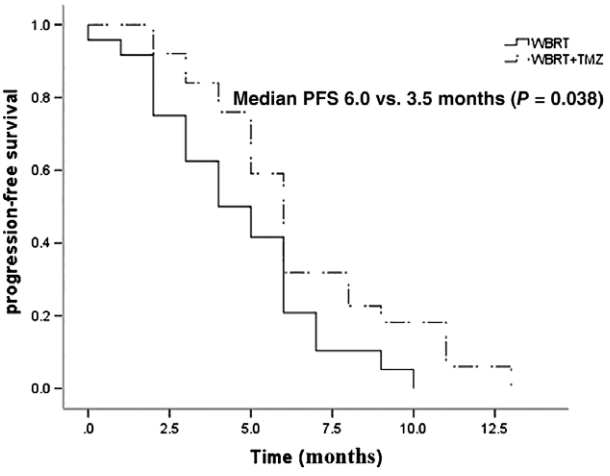

Figure 1 Kaplan–Meier progression-free survival (PFS) curve. TMZ, temozolomide; WBRT, whole brain radiotherapy.

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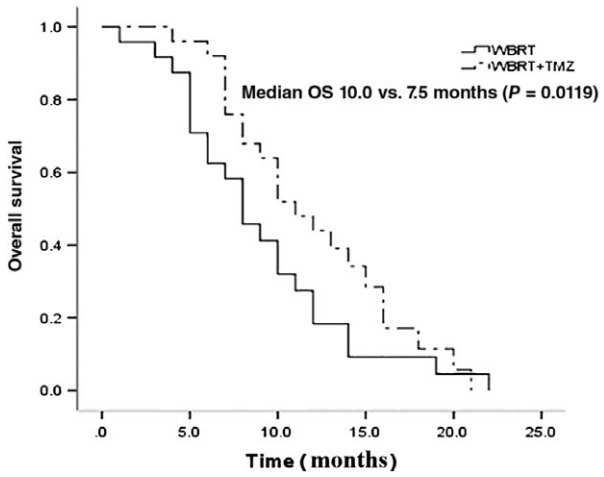

Figure 2 Kaplan–Meier overall survival (OS) curve. TMZ, temozolomide; WBRT, whole brain radiotherapy.

Discussion

The treatment of patients with BM from NSCLC continues to evolve. WBRT remains the primary treatment for patients with multiple BM (> 3); however, the efficacy of this treatment is not satisfactory. Patients eventually die of BM or the inability to control the metastasis of the primary tumor in another organ. Therefore, it is considered necessary to combine chemotherapy strategies to improve patient survival.

As a new, oral alkylating agent, TMZ can effectively break the BBB. Once it enters the CNS, TMZ is immediately converted into active metabolites, rapidly reaching effective concentrations in brain tissue. The bioavailability of TMZ is close to 100%.[8,9,15] Because TMZ induces tumor cell stagnation in the G2/M stage, the most sensitive stage of RT, and causes apoptosis, TMZ has a cytotoxic effect as well as an RT sensitization, which can improve the local control rate of BM.

Toxicity is particularly relevant in the treatment of BM, given the potential negative impact on QoL. TMZ dose-limiting toxicity is the result of an accumulation of bone marrow suppression; studies have shown that < 5% of patients experience bone marrow suppression during treatment. Therefore, it is unusual to delay the treatment time or adjust the dosage as a result of dose-limiting toxicity.

A phase II clinical trial comparing TMZ + WBRT with WBRT demonstrated that in most patients with BM, TMZ showed higher CR (38% vs. 33%; $P = 0.017$) and PR rates.[20] When TMZ was combined with WBRT, the ORR also improved.

In 2008, Addeo *et al.* used low dose delayed treatment of TMZ (75 $mg/m^2/d^1 \times 10$ days, then 75 $mg/m^2/d^1 \times 21$ days every 4 weeks, for a total of 12 cycles) in combination with WBRT.[21] The median OS and PFS was 8.8 and 6.0 months. A control group was not included, but the survival time of the patients treated with TMZ + WBRT was better than WBRT alone. To some extent, TMZ may be beneficial to the survival of patients with BM.

In our study, the addition of TMZ to WBRT in patients with BM significantly improved the ORR (TMZ + WBRT 91.1% vs. WBRT 66.7%; $P = 0.008$). Our results are consistent with those reported in previous studies, which demonstrated that TMZ + WBRT may enhance the overall ORR of NSCLC patients with BM compared to WBRT alone.[22] Our results suggest that TMZ + WBRT could significantly enhance median PFS compared to WBRT alone for the treatment of NSCLC patients with BM (6.0 vs. 3.5 months; $P = 0.038$), further suggesting that TMZ can improve the control rate of patients with BM. The median OS rates in the TMZ + WBRT arm and the WBRT arms were 10.0 and 7.5 months ($P = 0.143$), respectively. Although a trend toward better OS was observed with combination therapy in NSCLC patients with BM, the effect was not significant.

The addition of a daily TMZ dosing regimen to WBRT was well tolerated in our patient cohort. Headache and nausea were the most frequent side effects observed in both arms, followed by fatigue, vomiting, neutropenia, and thrombocytopenia. The TMZ + WBRT showed a trend of increased side effects compared to the WBRT arm, as reported in previous studies.[23,24] However, when neutropenia or thrombocytopenia developed, it resolved quickly and only resulted in minor treatment delays of up to a week. Gastrointestinal toxicity was tolerated with symptomatic support treatment; however a few ceased oral TMZ after support treatment failed.

Table 3 Incidence of hematological and non-hematological toxicity

	TMZ + WBRT (n = 45) (%)		WBRT (n = 33) (%)	
Toxicity	WHO Grade I–II	WHO Grade III–IV	WHO Grade I–II	WHO Grade III–IV
Hematological toxicity				
Leucocytes	7 (15)	3 (6)	2 (6)	0 (0)
Anemia	12 (27)	0 (0)	10 (30)	0 (0)
Neutrophils	16 (36)	5 (11)	1 (3)	0 (0)
Lymphocytes	10 (22)	5 (11)	4 (12)	2 (6)
Thrombocytes	23 (51)	7 (16)	16 (48)	1 (3)
Non-hematological toxicity				
Fatigue	25 (56)	6 (13)	15 (45)	5 (15)
Diarrhea	6 (13)	0 (0)	4 (12)	0 (0)
Nausea	27 (60)	8 (18)	11 (33)	4 (12)
Vomiting	20 (44)	7 (16)	15 (45)	6 (18)
Headache	30 (67)	0 (0)	21 (63)	0 (0)
Anorexia	21 (47)	5 (11)	10 (30)	0 (0)

TMZ, temozolomide; WBRT, whole brain radiotherapy; WHO, World Health Organization.

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Table 4 Neurocognitive and quality of life assessment compliance

	TMZ + WBRT arm		WBRT arm		
Assessment	Not evaluated	Received	Not evaluated	Received	*P*
HVLT					
Baseline	1	44	1	32	0.82
At 3 months	3	42	2	31	0.91
At 6 months	5	40	4	29	0.89
At 9 months	9	36	7	22	0.67
TMT					
Baseline	2	43	3	30	0.41
At 3 months	3	42	4	29	0.40
At 6 months	6	39	6	27	0.56
At 9 months	10	35	7	26	0.91
COWAT					
Baseline	1	44	2	31	0.38
At 3 months	4	41	4	29	0.64
At 6 months	5	40	7	26	0.22
At 9 months	8	37	10	23	0.20
FACT- L					
Baseline	4	41	3	30	0.97
At 3 months	5	40	5	28	0.60
At 6 months	7	38	6	27	0.76
At 9 months	9	36	8	25	0.67

COWAT, Controlled Oral Word Association Test; FACT-L, Functional Assessment Of Cancer Treatment-Lung; HVLT, Hopkins Verbal Learning Test; TMT, Trail Making Test; TMZ, temozolomide; WBRT, whole brain radiotherapy.

In our series cohort, we observed considerable improvement in QoL, measured using the HVLT, TMT, COWAT, and FACT-G questionnaires. The results of our QoL analysis showed a high level of satisfaction among patients treated with TMZ + WBRT treatment for BM, which provides excellent support for its acceptability. Our results indicate that adding TMZ for the treatment of NSCLC patients with BM could prevent the NCF and QoL from worsening at six months. These results also implied that TMZ, as maintenance therapy, may improve NCF and QoL. Similarly, a single-institution phase I clinical trial of patients with multiple brain lesions from breast carcinoma treated by capecitabine and TMZ demonstrated significant improvements in attention span ($P = 0.047$) and emotional function ($P = 0.016$), indicating that adding TMZ is not neurotoxic and may have a beneficial effect.[25] Addeo *et al.*

Table 5 Deterioration status from baseline in each examination using reliable change index

	TMZ + WBRT arm		WBRT arm		
Assessment	Deterioration	No deterioration	Deterioration	No deterioration	*P*
At 3 months					
HVLT	8	34	6	25	0.97
TMT	9	33	8	20	0.49
COWAT	7	34	8	21	0.29
FACT- L	8	32	7	21	0.62
At 6 months					
HVLT	9	31	14	15	0.026
TMT	9	30	13	14	0.035
COWAT	10	30	13	13	0.039
FACT- L	12	26	14	13	0.037
At 9 months					
HVLT	16	20	11	11	0.68
TMT	18	17	15	11	0.63
COWAT	20	17	13	10	0.85
FACT-L	20	16	15	10	0.73

COWAT, Controlled Oral Word Association Test; FACT-L, Functional Assessment Of Cancer Treatment-Lung; HVLT, Hopkins Verbal Learning Test; TMT, Trail Making Test; TMZ, temozolomide; WBRT, whole brain radiotherapy.

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also reported a statistically significant improvement in QoL at three, six and nine months for 59 patients treated by 30 Gy WBRT with concomitant TMZ.[21]

In summary, the ORR of 91% achieved with the combination of TMZ and WBRT is substantially higher than that previously reported for any other chemoradiotherapy regimen. Adding TMZ to WBRT for the treatment of NSCLC patients with BM could improve median PFS compared to WBRT alone; however, no remarkable difference in median OS was found. TMZ prevented NCF and QoL from deteriorating and the adverse effects of TMZ + WBRT were mild. Although the addition of TMZ increased the adverse effects, they were noncumulative and reversible with supportive treatment.

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Disclosure

No authors report any conflict of interest.

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