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Original Research Article

Concomitant treatment of brain metastases with whole brain radiotherapy and temozolomide protects neurocognitive function and improve quality of life

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Abstract

Purpose: *To study the protective effects of a combination of temozolomide (TMZ) and whole brain radiotherapy (WBT) on neurocognition, and its effect on the quality of life (QoL) in patients with brain metastasis (BM) from solid tumors, relative to WBT alone.*
Methods: *A total of 256 BM patients were enrolled and divided into two groups treated with either WBT plus TMZ, or WBRT alone. All patients received 30 Gy WBT, with or without concomitant TMZ (75 mg/m^2/day) during the irradiation period, and subsequently up to six cycles of TMZ (150 mg/m^2/day).*
Results: *The mean intracranial objective response (IOR) for all patients was 44.80 % while the IOR for WBT arm and WBT+TMZ group arm were 32.48 and 56.56 %, respectively (p = 0.03). The median intracranial overall survival (OS) for all the patients was 7.70 months. The median OS for WBT alone group (6.53 months) was significantly shorter than that of the WBT + TMZ arm (9.57 months). Statistically significant difference in quality of life (QoL) was observed between both arms at six months. Moreover, WBT+TMZ group had higher incidence of toxicity, when compared to WBT-only group.*
Conclusion: *These results suggest that co-application of WBT and TMZ improves intracranial ORR and median OS in BM patients, relative to the use of WBT alone. Although the side effects may be increased as a result of addition of TMZ, toxicity is tolerable and manageable.*

Keywords: *Brain metastasis, Temozolomide, Whole brain radiotherapy, Neurocognition*

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INTRODUCTION

The prognosis of BM which occurs in approximately 20 to 40 % of adult cancer patients, is usually poor [1,2]. Brain metastasis (BM) usually arises from primary malignancies of breast, lung, kidney and gastrointestinal origin [3]. Patients with untreated BM hardly survive beyond one month [1,4]. The treatment of BM involves inputs from several medical disciplines, and entails radiotherapy (whole brain), as well as surgical and systemic therapies [5].

Temozolomide (TMZ) is a new oral alkylating agent. The incorporation of TMZ to whole brain radiotherapy may improve the response rate of

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patients with brain metastases [6-10]. Previous studies have reported that patients suffering from glioblastoma [11,12]; breast cancer [13,14] and lung cancer [15,16] placed on a TMZ and WBT responded much better than patients receiving radiotherapy alone.

The present investigation was aimed at evaluating the effectiveness and safety of combining TMZ with WBT in the management of BM from solid tumors. The survival benefits, neurocognition and QoL of patients on WBT with or without TMZ were also evaluated.

METHODS

Subjects

Eligible patients were aged 18 to 80 years whose primary malignancies were confirmed through histology. Brain metastasis was confirmed by gadolinium-improved MRI or CT scan. The ECOG status of the subjects ranged between 0 and 3, and their biochemical and hematological profiles were within accepted ranges (leukocytes ≥ 3.5×10^9 /L, platelets ≥ 100×10^9 /L, bilirubin ≤ 25 μM, creatinine ≤ 150 μM, and creatinine clearance ≥ 60 mL/min). In addition, the enrolled subjects had no uncontrolled morbidities. The exclusion criteria covered subjects given prior medical attention for BM, patients with serious morbidities, as well as pregnant and breastfeeding patients. This research was approved by the Ethical Committee of Southern Medical University ((approval number = S2013-08-02), and it complied with the guidelines of the Declaration of Helsinki promulgated in 1964 as amended in 1996 [17]. All subjects gave signed informed consent prior to the treatments.

Study design and procedures

Patients were randomly assigned to receive WBT (127 cases), or WBT plus concomitant TMZ (129 cases). Conformal radiotherapy (parallel-opposite and lateral, 2) was given at a total dose of 30 Gy in 15 fractions for three weeks, along with oral TMZ (75 mg/m^2), given daily till the end of the radiation period. After a four-week break, patients received up to six cycles of adjuvant TMZ (150 mg/m^2) daily for five days every twenty-eight days.

Determination of neurocognitive function and QoL

Health-related neurocognitive function and quality of life were measured using revised Hopkins Verbal Learning Test (HVLT-R) and subject-completed Functional Assessment of Cancer Therapy (FACT), respectively. The HVLT-R is a learning and memory test in which the patient is asked to learn and recall a list of twelve words over three trials [18]. The FACT-General (FACT-G) version 4 is a twenty-seven-item package with a five-point Likert scale core multidimensional questionnaire for evaluating various domains of quality of life such as physical, functional, family, social, and emotional domains [19].

Treatment evaluation and definitions

Baseline assessment was performed weekly before the study. Weekly evaluations of progress response were carried out during concurrent treatment. Evaluation was carried out for four weeks after completion of treatment protocol for the first six months, and then every two months thereafter. It involved laboratory tests, brain CT or MRI and clinical evaluation, with objective response rate (ORR) as primary end-point, while the secondary endpoints involved overall survival (OS), neurocognitive function (NCF), and quality of life (QOL). Complete response (CR) referred to the absence of all traces of BM, while partial response (PR) referred to 50 % or greater reduction in quantifiable brain lesions (BL), or a clear improvement in quantifiable BL. The ORR referred to the percentage of subjects with decreased tumor size of a pre-defined degree within a definite time frame.

Statistical analysis

The baseline characteristics of the two groups were subjected to statistical analysis using Fisher's exact test or chi-square test, while survival was analyzed with the method of Kaplan-Meier. Log-rank test was used in comparing survival curves. All tests (two-sided) were performed using SPSS 23. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Characteristics of enrolled subjects

A total of 239 patients completed the treatment and were assessed for treatment effectiveness (122 in the WBT + TMZ group, and 117 in the WBT-alone group). The clinical, demographic, pathological and baseline disease characteristics of the patients are listed in Table 1. There were no significant differences between the two treatment groups.

Responses and survival of patients

A total of 239 patients were assessed for

responses. The average intracranial ORR for all patients was 44.77 % (107/239). Patients who received WBT plus TMZ had an ORR of 56.56 % while WBT alone patients had ORR of 32.48 %. The median IOS for all subjects was 7.7 months (95 % CI = 6.71 - 8.69 months). The median OS of the WBRT + TMZ group (9.57 months) was longer than that of the WBRT-alone group (6.53 months, $p = 0.001$).

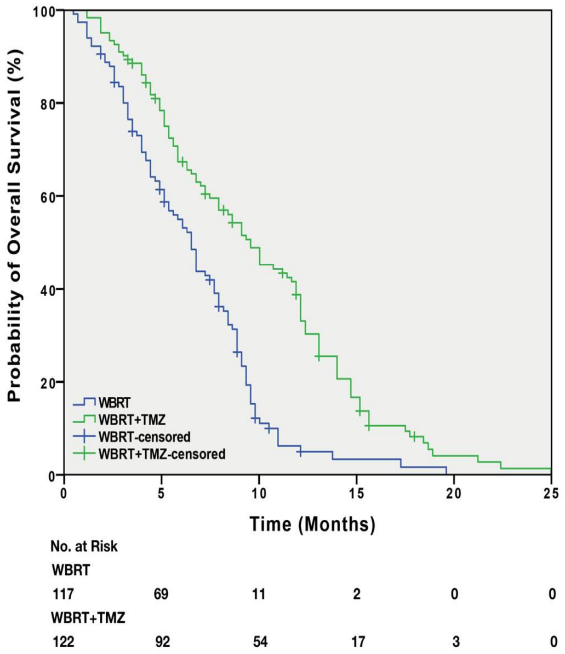

Figure 1: The overall survival of patients with brain metastases

Table 1: Baseline characteristics of BM subjects

Parameter	WBT+TMZ (%)		WBT (%)		Total		*P-value*
	No. of Patients (122)	*%*	*No. of Patients (122)*	*%*	*No. of Patients (122)*	*%*	
AGE							
>60	68	55.74	66	56.41	134	56.07	0.92
≤60	54	44.26	51	43.59	105	43.93	
Gender							
Male	68	55.74	68	58.12	136	56.9	0.71
Female	54	44.26	49	41.88	103	43.1	
KPS							
≥70	31	25.41	32	27.35	63	26.36	0.73
<70	91	74.59	85	72.65	176	73.46	
No. of BM							
>2	23	18.85	23	19.66	46	19.25	0.88
≤2	99	81.15	94	80.34	193	80.75	
Extracranial metastases							
Yes	33	27.05	35	29.91	68	28.45	0.62
No	89	72.95	82	70.09	171	71.55	
Primary disease control							
Yes	9	7.38	11	9.4	20	8.37	0.57
No	113	92.62	106	90.6	219	91.63	

Neurocognition function (NCF) and QoL

Table 3 shows deleterious changes over six months in line with Reliable Change Index threshold baseline. Prior to treatment, the scores for neurocognitive function and quality of life between the two groups were comparable ($p > 0.05$). There were 24 out of 79 evaluated patients for WBRT-plus-TMZ group with deterioration in FACT. The proportion of patients with deterioration in FACT was significantly lower in WBRT-plus-TMZ group than in WBRT-alone group ($p < 0.05$).

Adverse side effects

All the patients were assessed for tolerability and adverse effects and the results are presented in Table 4. At baseline, the WBT + TMZ and WBT-alone were comparable with respect to tolerability and adverse effects ($p < 0.05$). The predominant adverse effect was anemia (53.97 %), while, the most frequent non-hematologic adverse effect was asthenia (74.48 %). Except for headaches, no other major difference was observed both treatment groups.

DISCUSSION

The strategies used in the management of BM from solid tumors have continued to evolve. Management of brain metastases typically requires a multidisciplinary approach.

Table 2: Analysis of objective response rate in patients with brain metastases

Group	Parameter										Total	*P-value*
	CR	*%*	*PR*	*%*	*SD*	*%*	*PD*	*%*	*ORR*	*%*		
WBRT+TMZ	10	8.2	59	48.36	8	6.56	45	36.89	69	56.56	117	0.03
WBRT	5	4.27	33	28.21	12	10.26	67	57.26	38	32.48	122	
Total	15		92		20		112		107		239	

Data are objective response rate in WBRT + TMZ and WBRT alone on treated patients

Table 3: Deterioration over time relative to baseline, based on Reliable Change Index

Deterioration status	WBT+TMZ		WBT		*P-value*
	Deterioration	*No Deterioration*	*Deterioration*	*No Deterioration*	
At 3 months					
HVLT	14	89	17	74	0.33
FACT	16	87	20	71	0.25
At 6 months					
HVLT	26	53	19	35	0.79
FACT	24	55	26	28	0.04

Table 4: Deterioration status from baseline in each examination using reliable change index

Adverse event	WBRT+TMZ (N=122)		WBRT (N=117)		*P*-value
	Grade I/II	*Grade III/IV*	*Grade I/II*	*Grade III/IV*	
Hematologic					
Lymphopenia	43	2	38	1	0.64
Neutropenia	51	11	38	6	0.57
Anemia	71	4	53	1	0.31
Thrombopenia	58	4	44	0	0.23
Non-hematologic					
Asthenia	65	23	71	19	0.43
Nausea	64	25	60	17	0.37
Vomiting	56	9	50	8	0.99
Headaches	44	8	44	2	0.07

In the present study, the effectiveness of combination of TMZ and WBT on neurocognition and QoL in the treatment of different kinds of solid tumors with BM was investigated. The intracranial ORR of BM given WBT + TMZ was significantly higher than that of the WBT alone. These results are in agreement with those obtained in previous studies, where it was speculated that WBT + TMZ may enhance ORR [9,16]. The median OS in WBT-plus-TMZ group, and WBT group appear better than those reported in previous studies [10]. This improvement may be due to fact that there were more patients in RPA classes I and II in the present study. Considerable improvement in quality of life was also observed. These results suggest that WBT + TMZ can prevent the degenerations in neurocognitive function and quality of life within six months, and that TMZ may prevent tumor recurrence in the brain.

The higher incidence of adverse side effects in the WBRT + TMZ group is in agreement with previous reports. However, the observed variations in incidents of adverse events between WBT + TMZ, and WBR- alone groups was not statistically significant.

CONCLUSION

The use of whole brain radiotherapy plus concomitant TMZ to treat patients with brain metastases can improve their intracranial ORR and median OS better than the use of WBRT alone. Incorporation of TMZ to whole brain radiotherapy provides a significant and clinically important survival benefits. Although the side effects are increased following TMZ addition, the toxicities are tolerable and manageable. Thus, the concomitant administration of TMZ and whole brain radiotherapy may improve efficacy in patients with brain metastasis.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Xiaodan Jiang conceived and designed the study and revised the manuscript. Yufei Zhan performed the experiments, collected and analysed the data, wrote the manuscript. All authors read and approved the final manuscript.

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