Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i5.6251

TO EVALUATE THE CLINICAL EFFICACY OF WHOLE BRAIN RADIOTHERAPY CONCOMITANT WITH TEMOZOLAMIDE IN BRAIN METASTASES

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Abstract:

Objectives:

- To assess the Improvement in Signs and symptoms.
- To assess 90 days progression free survival
- To assess the Radiological response at day 30 and 90 with MRI brain.

Materials and Methods: In this Randomized control trial, total of 4o patients were enrolled. The enrolled patients were divided into two groups. Group A patients were treated with WBRT alone while Group B patients were treated with WBRT and TMZ. The radiologic response at Day 30 and the 90-day progression-free survival of the BM served as the main efficacy indicators.

Results: In our 40 patient study, 20 patients underwent RT alone and 20 received WBRT and TMZ. No statistically significant differences were found between the both groups. In 30 days response 2 (10.0%) patients shows complete response and 6 (30%) shows partial response in each group. 8 (40.0%) patients shows stable disease condition in group A while 9 (45.0%) patients shows progressive disease condition in group B patients. At 90 days, the radiologic response was assessed and it was noted that there was no statistically significant difference between the groups. **Conclusion:** Concurrent treatment of RT and TMZ was well tolerated and improved BM's 90day progression-free survival rate considerably. These findings indicate that TMZ might enhance local BM management, but caution should be exercised.

Key words: Temozolomide, Whole brain radiotherapy, Brain metastases.

INTRODUCTION:

The most frequent type of intracranial tumor, brain metastasis (BM), is a significant contributor to morbidity and mortality in cancer patients and affects 10–30% of adult cancer patients (1). Nonsmall cell lung cancer (NSCLC) and breast cancer deaths are both significantly influenced by BM (2). BM occurs at a rate of 30–40% in NSCLC (3). Patients with BM have decreased quality of life and have a poor prognosis. BM has been more frequent with time (4). This is most likely due to advancements in neuroimaging techniques and better systemic and primary tumor treatments, which have increased survival rates. Whole brain radiotherapy (WBRT) is a medical treatment used primarily in oncology to treat certain brain-related conditions, particularly when cancer has spread (metastasized) to the brain (5). WBRT is used to deliver radiation therapy to the entire brain (6). It's typically employed when multiple brain metastases are present, or when cancer has spread widely within the brain. The

goal is to slow down or stop the growth of cancer cells in the brain. Chemotherapy is still debatable as a treatment option for patients with BM, despite being the standard of care for treating disseminated NSCLC (7). The blood-brain barrier (BBB) prevents many powerful chemotherapy treatments from reaching the central nervous system (CNS), which is where they are most effective (8). Chemotherapy is still debatable as a treatment option for patients with BM, despite being the standard of care for treating disseminated NSCLC (9).

However, several academics have confirmed that BM can compromise the BBB's integrity (10). The BBB has been successfully penetrated by a number of novel chemotherapies in recent years, including paclitaxel, gemcitabine, Changchun Rubin, gefitinib, and temozolomide (TMZ).

Temozolomide (TMZ) is a chemotherapy medication primarily used in the treatment of certain types of brain tumors, particularly malignant gliomas (11). It is an oral alkylating agent, which means it works by interfering with the DNA in cancer cells, preventing them from dividing and growing (12). Temozolomide is a prodrug, which means it is converted into its active form in the body. The active compound causes DNA damage by adding methyl groups to the DNA strands, leading to the death of rapidly dividing cancer cells (12). Common side effects of temozolomide include nausea, vomiting, fatigue, and a decreased blood cell count (neutropenia and thrombocytopenia) (13). The concurrent use of WBRT plus TMZ followed by TMZ therapy in patients with newly diagnosed glioblastoma multiforme or BMs has been shown in clinical studies to be generally safe (14-16). Achieving disease control in 41% of patients with various initial malignancies, Abrey et al.(17) investigated the effectiveness of single-agent TMZ in the treatment of recurrent BM following WBRT.

Objective:

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- To assess 90 days progression free survival
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MATERIALS AND METHODS:

Study Design: Randomized Clinical Trial.

Study setting:

Duration of the study: Duration of the study was 3 years (Feb 2022 – Jan 2023).

Sample Size: 40 patients was selected out of which 20 patients received only whole brain radiotherapy 20 Gy in 05 fractions and 20 patients received concurrent chemotherapy with capsule temozolamide 75mg/m^2 with whole brain radiotherapy.

Sampling Technique: Non-probability

Consecutive sampling technique were used for the recruitment of patients.

Inclusion Criteria:

- Histo pathological proven malignancy of any site.
- Measurable multiple brain metastases confirmed by MRI Brain.
- Adequate Hematological and Hepatic functions.

Exclusion Criteria:

- Age 18 to 60 years.
- Hematological Malignancies.
- Prior treatment for brain metastases.
- Single brain metastasis.

Methods:

After the approval of ethical committee of CPSP and department of Radiotherapy, IRNUM Hospital, Peshawar, patients diagnosed according to our inclusion criteria were enrolled. Forty patients were enrolled. The enrolled patients were divided into two groups. Group A patients were treated with WBRT alone while Group B patients were treated with WBRT and TMZ. WBRT was

administered five times per week in 10 doses of 3 Gy for a total dosage of 30 Gy, using megavoltage radiation to cover the entire cranium with two isocenter parallel and opposing fields. TMZ was administered at a rate of 75 mg/m2/d during RT, 5 days per week for 2 weeks, and then twice every 28 days at a rate of 200 mg/m2/d for 5 days (150 mg/m2 in patients who had received a lot of pretreatment). There was a 4 week gap between the end of concurrent treatment and the 5-day cycles of TMZ. TMZ was given under fasting conditions for at least one hour prior to and one hour following treatment. The subsequent cycle of chemo- therapy was delayed until patients achieved an absolute neutrophil count ≥1.5 × 109/L and platelet count ≥100 × 109/L and non- hematologic toxicities had resolved to Grade 1 or less. Treatment was deferred for a maximum of 3 weeks to allow toxicity recovery. A 25% dose reduction was instituted when the patient experienced Grade 3 or 4 toxicity. To maintain neurologic stability, a 4 mg/d dose of dexamethasone was given.

Statistical Analysis: By using the SPSS version 25.0, all the collected data were analyzed. The results were presented in the form of table and graph.

RESULTS:

In our 40 patient study, 20 patients underwent RT alone and 20 received WBRT and TMZ. Table 1 lists the patient characteristics for the two therapy modalities. A total of 17 (42.5%) were male while 23 (57.7%) were female patients. The mean age of Group A and Group B patients were 45.90 ± 10.0 and 49.9±8.63 years respectively (Table 2). All patients who had been enrolled had their radiologic response assessed on day 30, with 20 receiving WBRT and 2 receiving WBRT + TMZ. No patient was excluded away, and the mortality rate was also nil. No statistically significant differences were found between the both groups. In 30 days response 2 (10.0%) patients shows complete response and 6 (30%) shows partial response in each group. 8 (40.0%) patients shows stable disease condition in group A while 9 (45.0%) patients shows progressive disease condition in group B patients (Table 3). At 90 days, the radiologic response was assessed and it was noted that there was no statistically significant difference between the groups (Table 4).

Table 1: Distribution of patients according to gender *(n=40)*

Variable	**Frequency**	**Percentage**
Gender:		
Male	17	42.5
Female	23	57.5
Total	40	100%
	Mean	**SD**
Age	47.9	9.47

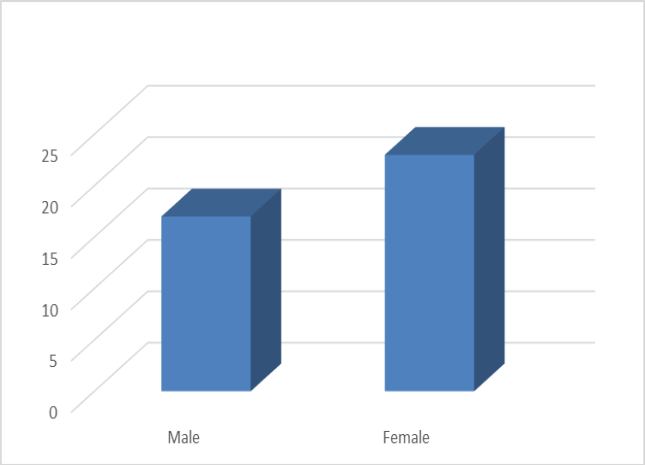

Figure 1: Graphical Representation of gender

Table 2: Patient characteristics on the basis of group *(n=40)*

Variables	Groups	
	A	B
Gender		
Male	8 (47.1%)	9 (52.9%)
Female	12 (52.2%)	11 (47.8%)
Age (Years)	45.90 ± 10.0	49.9±8.63
Duration of symptoms (Month)	2.04±0.81	2.40±1.14

Table 3: Radiologic response of brain metastases at 30 day *(n=40)*

Variables	Groups	
	A	B
Complete Response	2 (10.0%)	2 (10.0%)
Partial response	6 (30.0%)	6 (30.0%)
Stable disease	8 (40.0%)	9 (45.0%)
Progressive disease	4 (20.0%)	3 (15.0%)

⋆ P-value = 0.977 not significant

Table 4: Radiologic response of brain metastases at 90 day *(n=40)*

Variables	Groups	
	A	B
Complete Response	0 (0.0%)	1 (5.0%)
Partial response	3 (15.0%)	7 (35.0%)
Stable disease	6 (30.0%)	8 (40.0%)
Progressive disease	11 (55.0%)	4 (20.0%)

⋆ P-value =1.04 not significant

Discussion: In this double-blind, randomised clinical trial, we investigated the safety and efficacy of WBRT and TMZ combination therapy against WBRT alone when treating BMs in patients with solid tumours. In the experimental arm, we found no unanticipated toxicity. The number of objective responses did not increase when WBRT and TMZ were combined. The results of this trial support earlier findings that the combination of TMZ with WBRT is well tolerated and does not result in unexpected acute neurologic toxicities (13–15). In the combined treatment arm, there was a statistically significant rise in the radiologic responses (complete and partial responses). However, overall survival rates in both arms were comparable. The same authors [(18)], who used the same dosages of TMZ and WBRT in the present investigation, recently completed a Phase III trial with 134 eligible patients. Once more, they observed that there was no effect on overall survival despite a statistically significant rise in objective responses in the TMZ and WBRT. In comparison to their Phase III trial, we noticed a reduced frequency of responses in the experimental arm. Because most of our patients had already tried different forms of chemotherapy without success, it's possible that the BM was more resistant to TMZ, which could account for the decreased response rate of the WBRT and TMZ combo in our trial. Additionally, as evidenced by the patients' outcomes, our patients had more aggressive disease, which progressed quickly in the first month of treatment. Several studies have made an effort to enhance the outcomes of RT alone by contrasting normal fractionation with various RT timings, but they have not found any advantages of one procedure over another. Recent years have seen an increase in interest in combined therapies for BM, however there are still few

published randomized studies that use radiation sensitizers. Due to the inclusion of patients with advanced primary tumours or extracranial metastases, these trials did not demonstrate a beneficial effect on overall survival. Mehta and colleagues conducted a Phase III trial of patients with BM from solid tumours following WBRT with or without motexafin gadolinium, a redox modulator that increases apoptosis, in a recently published randomised trial. In the treatment arm, there were no statistically significant changes in overall survival or the time before neurologic progression. In a different study, the concurrent administration of WBRT and RSR13, a synthetic allosteric haemoglobin modifier that boosts tumour oxygenation, resulted in a statistically significant median survival advantage of 2.3 months when compared to the patient survival of the Radiation Therapy Oncology Group RPA BMs database (19).

Conclusion: The positive effects of TMZ when given along with WBRT in the response rate of BMs were not successfully replicated in the current study. We concluded that the combination of RT and TMZ therapy is secure, well-tolerated, and may even stall the progression of BM. Further studies are required to investigate the results.

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