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Original Research Article

Addition of temozolamide as radiosensitizer in brain metastasis: experience from a resource limited centre in sub-Himalayan region

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ABSTRACT

Background: Brain metastasis is a common, debilitating and undesirable neurological complication of systemic cancer and a significant cause of morbidity and mortality.
Methods: 39 patients of brain metastasis with Ca breast/Ca lung as primaries were randomized into a study arm and control arm in between 1st August 2018 to 31st July 2019 at IGMC Shimla. Control arm consisted of WBRT (30 GY/10 fractions/5 days a week). Study arm consisted of WBRT with same dose and temozolamide administered 75mg /m2/day during RT days.
Results: Out of 39 patients 34 patients completed treatment out of which 17 in study and 17 in control arm. Response to brain lesions could not be assessed in 20 out of 39 patients. In remaining 19 patients 36.8% patients in study arm and 20% patients in control arm had partial response (PR). 5.3% patient in study arm and none in control arm has complete response (CR). 25% patients in control arm and 15.8% patients in study arm had stable disease. Improvement in QOL (FACT- G) seen in both study and control arm post Rx, however improvement sustained in study arm at 1st F/u.
Conclusions: Leveraging the additional radio-sensitizing effect of TMZ may hold promise as an attractive strategy to enhance the quality of life in patients with a favourable performance status. Moreover, RPA could serve as a decisive factor in tailoring the treatment approach, guiding the choice between palliative radiotherapy and best supportive care for these individuals.

Keywords: WBRT, Temozolamide, Brain-mets, MBC, Metastatic lung cancer

INTRODUCTION

Brain metastasis is a common and undesirable neurological complication of systemic cancer Median time for diagnosis stands at 8.5 to 12 months from primary diagnosis. Lung cancer followed by breast cancer constitute most common primary cancer associated with BM with association of 20-50% and 5-20% respectively. Chemotherapy has a limited role in treatment of brain mets because of presence of blood brain barrier.[1] Use of radiotherapy (Whole brain Radiotherapy) and surgery are the mainstay treatment for the management of many metastatic lesions in the brain, particularly if they become symptomatic; however, these modalities have many limitations depending on the location and characteristics of the tumour.

Efficacious therapies that can be administered systemically to avoid such pathological effects on the brain are scarce, due in part to limitations on brain uptake

imposed by the blood–brain barrier (BBB). Treatment choices are limited: Patients with single brain metastasis are more likely to benefit from surgery/radiosurgery. Stereotactic Radiosurgery is emerging as an increasingly attractive treatment option, particularly with the advent of advanced machines like Cyberknife. This approach holds particular promise for young patients with good performance status and effective control of extracranial metastasis, making it a compelling therapeutic choice. The presence of multiple metastasis often preludes the option of surgical resection. Mostly palliative approaches are part of the standard treatment to relieve the neurological symptoms particularly the use of corticosteroids and anticonvulsants. WBRT i.e., whole-brain radiotherapy is the standard of treatment with >5 lesions. It results in the median survival of 4 to 6 months and improves neurological function in most of the cases. Temozolamide is an oral alkylating agent with excellent CNS penetration. It has shown promise as a radio sensitizer in some trials.[2]

Objectives

Objectives were to compare the efficacy of the combination of Temozolamide and WBRT in patients with previously untreated Brain mets (from NSCLC and Breast cancer) vs. WBRT alone. Primary endpoints were response to the brain lesions post treatment and QOL.

METHODS

This was an observational case control study conducted in department of radiation therapy and oncology in Tertiary cancer centre, IGMC Shimla from 1 August 2018 to 31 July 2019. Informed consent was taken from all patients for enrolment into the study.

Inclusion criteria

All the adult patients with Age ≥18 years and ≤75 years diagnosed with brain metastasis from lung cancer and breast cancer (histologically proven primary cancer) with measurable multiple brain metastasis assessable by gadolinium enhanced MRI were included in the study from August 2018 to July 2019 in our tertiary cancer centre, IGMC Shimla located in northern India. Inclusion criteria consisted of patients with KPS ≥ 60, previously untreated patients for brain metastasis and normal CBC, LFT, RFT at baseline. Those patients who are not suitable for surgery/radiosurgery or suitable but denied the same were included in the study.

Exclusion criteria

Patients with Age >75 years, any primary apart from NSCLC/CA breast, history of prior treatment for brain metastasis, severe intercurrent medical illness/ symptomatic heart disease, pregnant/lactating women, history of any surgery/radiosurgery in past for brain metastasis, diagnosed as unknown primary tumour and KPS <60 were excluded from the study

39 patients fulfilling the inclusion criteria were randomized into study arm and control arm. Control Arm/WBRT Alone arm consisted of WBRT 30 GY/10 fractions/5 days a week, one fractions each day on 5 consecutive days from Monday to Friday. Study Arm consisted of WBRT (30 GY/10 fractions/5 days a week, one fractions each day on 5 consecutive days from Monday to Friday) plus Temozolamide administered 75mg /m2/day during RT days 1 hour before RT. Whole brain Radiation therapy was given by Theratron® 780e or Equinox™ Cobalt-60 machines. Thermoplastic cast was utilized for immobilization in all the patients. Image 3 shows patient setup at equinox cobalt 60 machine for WBRT. All patients received corticosteroids and anticonvulsants only when necessary. Patient evaluation consisted of complete physical examination including detailed neurological examination weekly during concurrent treatment. Complete blood profile was done weekly during the treatment and haematological toxicities were noted. MRI for knowing response to the therapy was performed in both the arms 45 days after completion of WBRT. Response Evaluation by RECIST CRITERIA 1.1 was utilized to know the response to the lesions. QOL evaluation by FACT-G (Functional Assessment of Cancer Therapy) Version of Questionnaires was performed at baseline, during treatment, completion of treatment and 1st follow up.

RESULTS

The data was keyed into Microsoft excel spreadsheet and cleaned for any inaccuracies. and statistical analysis was done using IBM SPSS Statistics for Windows. Categorical variables were shown in the form of frequencies and percentages. Among 39 patients, more patients were there in <65-year age group (Table 1). Number of male patients were more than female. More number of patients presented with lung cancer as a primary than breast cancer. Among CA lung patients a greater number of patients had adenocarcinoma histology. Out of 39 patients, 21 patients had Karnofsky Performance Score (KPS) of <70 and 18 patients had KPS >70. Majority of the patients had RPA class 3. Response was evaluated using RECIST criteria with PR 36.8% vs. 20.0%, CR 5.3% vs. 0.0% SD 15.8 % vs. 25.0% in study and control arms respectively but it was not statistically significant (Figure 1-4). Quality of life was assessed using FACT G Questionnaire. There was a trend towards improvement in score in both study and control arm at completion of treatment and 1st follow up, however the trend persisted in the study arm even in the first follow up (Figure 5). Mean progression free survival was 67.75 days (=2.2months) in the control arm (WBRT) and 108.58 days (=3.5 months) in the study arm (WBRT+TMZ) with non-significant p value of 0.145. In our patients, survival was 5.2 months,2.7 months and 2.04 months respectively for RPA class I, II and III and was statistically significant (p=0.036). There were comparable haematological toxicities (CTCAE criteria) in both arms with grade 2 toxicity seen only in two patients in 2nd week in study arm and one patient in control arm.

Table 1: Patient characteristics and details of brain lesions at presentation.

Patients characteristics	Control	Study	Total
Age			
<65	15	12	27
>65	5	7	12
Sex			
Male	14	7	21
Female	6	12	18
Primary			
Lung	17	12	29
Breast	3	7	10
Histology			
Sq.CC	8	3	11
Adeno-Ca	9	9	18
Invasive ductal cell	3	7	10
KPS			
<70	10	11	21
>70	10	8	18
RPA			
I	4	3	7
II	6	8	14
III	10	8	18
Extra-cranial mets			
Present	6	10	16
Absent	14	9	23
Upfront brain mets			
Yes	8	6	14
No	12	13	25
No. of brain lesions			
<3	12	11	23
3-5	4	2	6
>5	4	6	10
Midline shift			
Yes	7	4	11
No	13	15	28
Size of brain lesions (Max) (cm)			
<3	12	10	22
3-5	5	8	13
>5	3	1	4

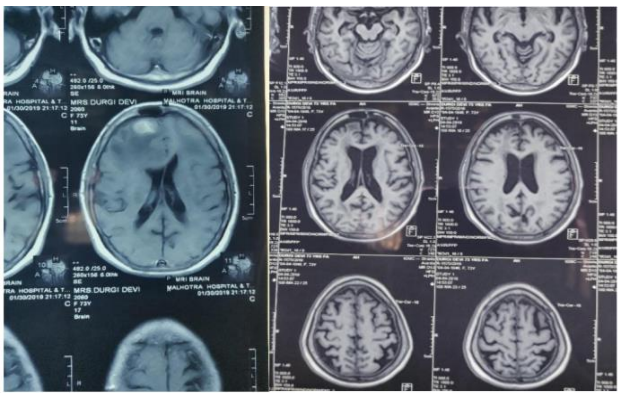

Figure 1: MRI image- pre-treatment image showing brain metastasis in right frontal region.

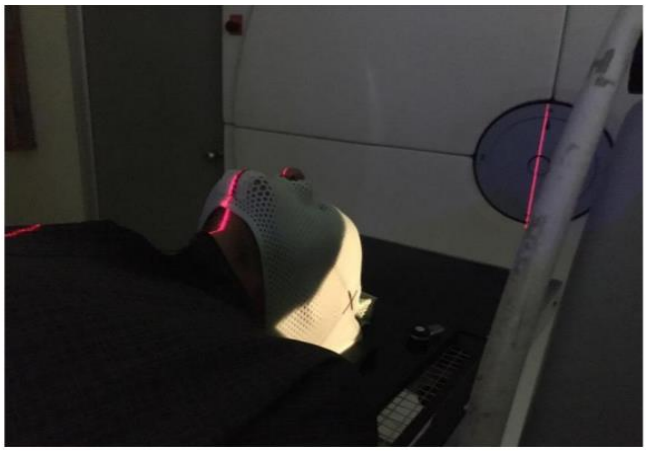

Figure 2: MRI image.

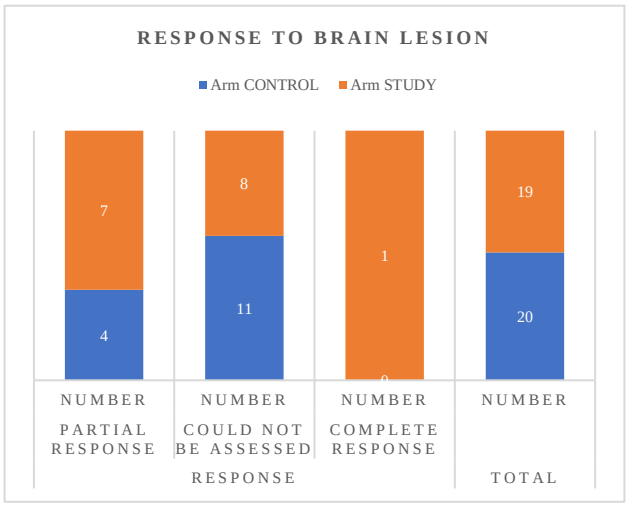

Figure 3: Response to brain lesions as assessed by MRI 45 days post RT completion. Response could not be assessed in 19 patients due to either death before 1st follow up or poor general condition.

Figure 4: Patient with setup at equinox cobalt 60 machine for WBRT.

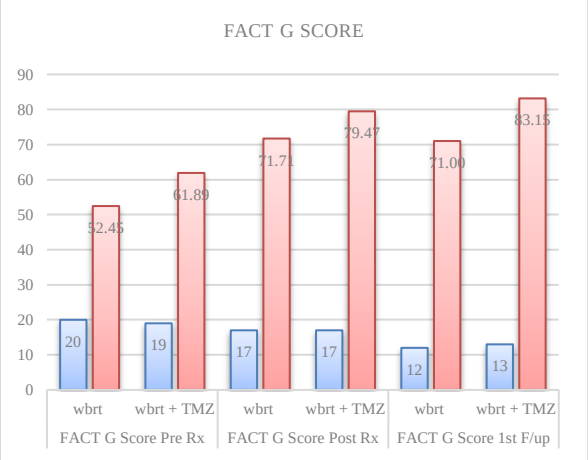

Figure 5: QOL as assessed by FACT G Questionnaire. Improvement in QOL seen in both study and control arm post Rx, however improvement sustained in study arm at 1st F/u.

DISCUSSION

Brain metastasis is a dreaded complication affecting many patients with end stage malignancy. These events are a major source of morbidity and can significantly decrease a patient's quality of life. Improvement in survival outcomes in patients with BM remains a big challenge for the oncologists, despite the advent of stereotactic radiotherapy and novel chemotherapeutic agents available. In a country like ours, very few centres are equipped with stereotactic radiotherapy equipment, and none is available in our State. Therefore, WBRT is the best radiotherapy treatment offered to patients of BM in developing countries including ours. Adding temozolamide being a radiosensitizer has shown promise in few trials. Antonadou et al in their study had concluded that Temozolomide is safe, and a significant improvement in response rate was observed when administered in combination with radiotherapy in patients with previously untreated brain metastases.[3] In our study, 39 patients of brain metastasis with primary in lung (NSCLC)/Breast were randomized to receive WBRT 30 GY/10 fractions/2 weeks (control arm=20 patients) and the patients in study arm (study arm=19 patients) in addition received Temozolamide 75mg/m2/day during RT days along with WBRT. No additional cycles of TMZ were given in these patients in both the arms.

Clinical Studies like Addeo et al have evaluated that the combination of WBRT and TMZ has significant clinical activity in the patients of brain metastasis from solid tumors. Fractions 30 GY WBRT was given with concomitant TMZ (75mg/m2/day) for 10 days and subsequently 150 mg/m^2/day×5 days every 28 days post RT for maximum of 6 additional cycles.[4] They reported 44% Overall response rate (CR+PR) and 8.5% CR and 76% brain disease control rate which were encouraging. The responses were independent of primary tumor, gender, previous chemotherapy. Unfavourable factors for response included KPS>70, age >65, presence of extra cranial metastasis and RPA Class III. In a study published in Bangladesh by Ali et al they concluded that the concurrent treatment with whole brain radiotherapy (WBRT) and temozolomide (TMZ) in patients with brain metastasis is well tolerated with an encouraging response. The overall response rate was 45%.[5]

Gamboa-Vignolle et al in their phase II trial studied efficacy of TMZ. Fifty-five patients were randomised into the following groups: 28 patients received WBI (30 GY in 10 fractions over 2 weeks) concomitant with once-daily 200 mg TMZ on Mondays, Wednesdays, and Fridays, and 300 mg TMZ on Tuesdays and Thursdays (TMZ plus WBI arm). Twenty-seven patients received the same schedule of WBI alone (control arm). They reported The objective response (OR) was 78.6% for the TMZ plus WBI arm, and 48.1% for the control arm (p=0.019).[6] In our study we considered TMZ only on RT days from Day 1 to Day 5 with dose of 75 mg/m^2 in study arm.

In our study the aim was to compare the efficacy of the combination of Temozolamide and WBRT in patients with previously untreated Brain mets (from NSCLC and Breast cancer) vs WBRT alone with primary endpoint was to investigate and compare the response of brain lesions to treatment and Quality of life in between both the arms. In this study response was evaluated using RECIST criteria with PR 36.8% vs. 20.0%, CR 5.3% vs. 0.0%, SD 15.8 % Vs 25.0% in study and control arms respectively but it was not statistically significant. In large number of patients, the response could not be evaluated 42.1% in study arm (8 out of 19 patients) and 57.9 % (11 out of 20 patients) in control arm. The reasons being death before response assessment (which was done with the help of MRI Brain at approximately 45 days from completion of treatment), inability to report to the institution for response assessment due to very poor KPS or reported but unfit for MRI Brain due to poor general condition/KPS.

In the research article by Xia Deng et al[7] about of 485 patients enrolled 247 had to be excluded from the study as some of them had lost to follow up/died within one month/did not finish WBRT or got surgery for brain metastasis. It is approximately 51% of total enrolment in the trial.

Zhu et al concluded that 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.[8] Adding TMZ to the treatment strategy could prevent neurocognitive function and quality of life from deteriorating. In our study post analysis of FACT G Score for QOL assessment there was a trend towards improvement in score in both study and control arm at completion of treatment and 1st follow up, however the trend persisted in the study arm even in the first follow up. Similarly in study by Addeo et al there was significant improvement in quality of life (p<0.0001) demonstrated by FACT-G analysis. Intent of dreaded brain

mets especially in areas of resource and financial constraints along with unavailability of advanced RT techniques is only palliation with good quality of life and addition of TMZ may provide a useful treatment strategy in such settings. Temozolamide has been earlier used in treatment of GBM along with radiation and as well as in adjuvant setting. It is a methylating agent with clinical activity against brain tumors, demonstrated excellent antitumor activity following administration to athymic mice bearing human brain tumor xenografts and was highly effective against intracerebral implants of the U251 and SF-295 glioblastomas.[9]

Van Nifterik KA et al in their study on TMZ-sensitive GBM cell lines shows that TMZ can act as a radiosensitizer and is at least additive to gamma-irradiation. Enhancement of the radiation response by TMZ seems to be independent of the epigenetically silenced MGMT gene.[10] Thus utilizing the potential of TMZ as a radiosensitizer in brain metastasis in WBRT served as a base in various studies aiming at improving the symptoms and QOL of patients suffering from brain metastasis. Veger et al in their study concluded that the concomitant use of RT with TMZ was well tolerated and resulted in significantly better progression-free survival of BM at 90 days.[11] Although caution should be used, these results suggest TMZ could improve local control of BM. In our study the mean progression free survival was 67.75 days (=2.2months) in the control arm (WBRT) and 108.58 days (=3.5 months) in the study arm (WBRT+TMZ) with non-significant p value of 0.145.

Antonadou et al in their study yielded a median OS of 8.6 months in TMZ +WBRT arm. The main issues encountered in our study were the total number of patients for the response assessment by MRI were approximately half of the number enrolled due to various reasons mentioned above especially death before 1.5 months / very poor KPS at the time of response assessment. Proescholdt et al in a systematic review of Neurosurgical Aspects of management of brain metastasis concluded that the surgical resection of a metastatic tumor reduces mass effects and the intracranial pressure, leading to prolonged overall survival. In this review other techniques like role of laser interstitial thermal therapy (LITT) and SRS were also highlighted.[12] Worldwide the median survival in RPA class I to III stands between 7.1,4.2 and 2.3 months and in our patients, it was 5.2 months, 2.7 months and 2.04 months respectively for RPA class I, II and III. Being the only institution in the State providing radiotherapy facility, with other centres at their infancy for RT administration, BM represents a significant proportion of the total palliative radiotherapy workload in the RT centre. In one of the retrospective study at our centre median survival was found to be 3.7 months (0.03 to 21.9 months).[13]

The study faced several limitations that warrant acknowledgment. Firstly, response assessment was hindered in approximately half of the patients due to various reasons, including mortality before the first follow-up or poor general condition at the time of the initial evaluation. This limitation is not uncommon, given the overall dismal survival rates observed in patients with brain metastases, as evidenced even in larger-scale studies like Deng et al.

Another significant constraint was the necessity to restrict our treatment approach to conventional 2D techniques. This limitation arose due to the unavailability and unaffordability of more advanced radiotherapy techniques, such as 3D conformal RT, VMAT, and stereotactic radiosurgery, in our centers. As observed in a planning study supporting the AROMA (A Randomised trial to Optimise outcomes in patients with multiple or large brain Metastases) clinical trial conducted by Chen et al, VMAT plans demonstrated the potential for higher doses to be delivered to brain metastases while minimizing doses to organs at risk (OARs).[14] Dose-escalated VMAT for larger lesions presented an opportunity to administer increased radiotherapy doses to such lesions while ensuring the safety of nearby critical structures. Despite these limitations, the study's findings provide valuable insights into the potential benefits of TMZ as a radio-sensitizer in patients with a favourable performance status. Additionally, the role of RPA in guiding treatment decisions between palliative radiotherapy and best supportive care highlights its significance in optimizing patient outcomes. However, future investigations using more advanced RT techniques and larger sample sizes are essential to further validate and refine these observations, potentially enhancing treatment efficacy and patient well-being.[15]

Bodensohn et al recently published their study comparing Stereotactic radiosurgery (SRS) to whole-brain radiotherapy (WBRT) in patients with 4-10 brain metastases. The study found that SRS was well-tolerated, with no grade III toxicities reported. However, the primary endpoint of demonstrating superior overall survival (OS) with SRS compared to WBRT did not reach statistical significance, as the hazard ratio was 0.65 (95% CI 0.40-1.05), with a p value of .074.

CONCLUSION

Given the aforementioned practical challenges, the identification of patients based on prognostic factors (such as RPA) becomes crucial to discern those who would truly benefit from WBRT versus those who may only require best supportive care. For those patients deemed suitable for WBRT, leveraging the additional radio-sensitizing effect of TMZ could potentially serve as an appealing strategy to enhance their quality of life.

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