Original Article

 Pak Armed Forces Med J 2013; 63 (2): 249-253

THERAPEUTIC EFFECTS OF WHOLE BRAIN RADIOTHERAPY WITH CARBOPLATIN AS RADIATION SENSITIZER IN MANAGEMENT OF BRAIN METASTASIS

Zeeshan Ahmed Alvi, Ahsan Mahmood, Usman Ali, Shahid Rasul, Salman Arif, Talha Maqsood, Saira Ahmed*, Saima Ishtiaq

Combined Military Hospital Rawalpindi, *Military Hospital Rawalpindi

ABSTRACT

Aim: To determine the efficacy of whole brain radiotherapy (WBRT) with carboplatin as radiation sensitizer in metastatic brain disease in our adult population.

Study Design: Quasi-experimental study.

Place and Duration: Department of Oncology, Combined Military Hospital (CMH), Rawalpindi, Pakistan from July 2011 to September 2012.

Patients and Methods: Forty two patients with metastatic brain disease having ECOG performance status (PS) 3 or less with normal hematological and biochemical profile were treated with WBRT with 6MV Photon beam on linear accelerator using parallel opposed lateral beams to a dose of 30 Gys in 10 fractions. Carboplatin was administered in a dose of 150 mg/m^2 on day 1 and 6 of WBRT. Improvement in PS and radiological response on CT scan/ MRI brain before and 30 days after the WBRT using response evaluation criteria in solid tumors (RECIST) was evaluated.

Results: Out of 42 patients, 38 (90%) showed improvement in PS, 4 (10%) showed either no improvement or worsening of PS (p< 0.001). Seventeen (41%) patients had complete response, 19 (45%) had partial response, 3 (7%) showed stable disease and 3 (7%) had progressive disease. None of the patients showed grade 3/4 toxicity during treatment.

Conclusion: WBRT with carboplatin as radiation sensitizer is effective in palliation of patients with metastatic brain disease.

Keywords: Brain metastasis, Whole Brain Radiotherapy, Carboplatin.

INTRODUCTION

Brain metastases are the most common intracranial neoplasm in adults and are a significant cause of morbidity and mortality. It affects 20-40% of all cancer patients and its incidence is increasing primarily because of improvements in diagnostic and therapeutic approaches[1]. Common clinical features include headache, neurological deficit, and seizures. The intent of treatment is palliative at this stage with aim to improve both quality and quantity of life.

There are many ways of palliation including corticosteroids, anti-epileptics, surgery, radiotherapy or stereotactic radio-surgery. Most often opted therapy in multiple brain metastases is corticosteroids along with radiotherapy as it is non-invasive, cheap and easily available[2]. For the majority of patients, most of whom have multiple metastases, WBRT (whole brain radiotherapy) remains the standard of care[3].

Although reports of the response rate after WBRT alone vary, complete responses (CRs) or partial responses (PRs) have been documented in approximately 60% of patients in randomized controlled studies[4]. Several fractionation schedules of WBRT are currently used in clinical practice. The results of meta-analyses suggest that differences in dose, timing, and fractionation do not significantly alter the median survival times of patients receiving WBRT for brain metastases[5].

Chemotherapy has traditionally played a limited role in the treatment of brain metastases. Uncertainty regarding the usefulness of chemotherapy for brain metastases is primarily

Correspondence: Dr Zeeshan Ahmed Alvi, Oncology Department, CMH Rawalpindi.
Email: zeeshanahmedalvi@yahoo.com
Received: 13 Dec 2012; Accepted: 14 Feb 2013

based on concerns that most agents do not cross the blood–brain barrier (BBB). Results of various studies on WBRT with radiosensitizers in brain metastases are varied and these agents will likely play increasingly important roles in the treatment of brain metastases[3].

Carboplatin is a radiosensitizing chemotherapeutic agent that crosses BBB[6]. This study was carried out to analyze the efficacy of WBRT with carboplatin as radiation sensitizer both in terms of symptom palliation, assessed by improvement in performance status, and objective response rate.

PATIENTS AND METHODS

This study was conducted between July 2011 to September 2012 at the Department of Oncology, Combined Military Hospital (CMH), Rawalpindi, Pakistan. It is phase-2 prospective non-randomized clinical trial. The following criteria were used to enroll patients in the study.

Inclusion criteria

1. Patients with histologically or radiologically confirmed brain metastases (by CT Scan or MRI Brain) from primary extra-cranial solid tumor.
2. Patients with age ≥ 18 and ≤70 years.
3. Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 3 or less.
4. Patients with expected survival ≥ 2 months.

Exclusion criteria

1. Patients with more than one malignancy.
2. Patients who have received previous WBRT.
3. Patients with abnormal hematological profile, liver or renal function.

With the approval from the Hospital Ethical Committee, 42 patients from Oncology out patient department (OPD) at CMH, Rawalpindi were enrolled in the study after obtaining their informed written consent. WBRT was given using two opposing right and left lateral fields, with 6 MV X-rays beam from linear accelerator, to a total dose of 30 Gys in ten fractions, five fractions a week, over a period of two weeks. Intravenous Carboplatin infusion was given at a dose of 150 mg/m^2 over two hours with pre-treatment with antiemetic and steroids on day 1 and 6 of WBRT. Radiological studies (CT scan or MRI brain) and ECOG PS were recorded at baseline before intervention and at 30 days after completion of treatment.

Data analysis was done with the help of the Statistical Package for the Social Sciences (SPSS) version 19 software. Marginal homogeneity test was used to compare pre and post treatment ECOG PS. Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess radiological response of treatment. Chi-square test was applied to compare response rates seen in brain metastases from different primary sites, p value of <0.05 was considered statistically significant.

RESULTS

The demographic characteristics, like age, sex and site of primary tumor of 42 patients enrolled in the study are shown in table 1. Breast carcinoma was the most common malignancy presenting with brain metastases in the study (62%) followed by lung carcinoma (28%). Before intervention 32 patients (76%) were having ECOG PS 3, 6 patients (14%) had ECOG PS 2, while 4 patients (10%) had ECOG PS 1. After one month of WBRT with carboplatin only 2 patients (5%) had ECOG PS 3 while 12 patients (28%) and 28 patients (67%) had ECOG PS of 2 and 1 respectively. Thirty eight patients (90%) showed improvement in ECOG PS whereas only 4 patients (10%) either had decline or no change in PS. This difference was statistically significant (p=0.001). Seventeen patients (41%) showed complete response (CR), 19 (45%) showed partial response (PR), 3 (7%) had stable disease (SD) while progressive disease (PD) was shown by 3 (7%) patients. Among patients with breast carcinoma, 31% patients showed CR, 54% showed PR and 15 % had either SD or PD. In

lung carcinoma patients CR and PR were seen in 67% and 33% patients respectively (p=0.078). No grade 3/4 hematological toxicities were observed in any patient. Only 2 patients (5%) developed grade 2 neutropenia and 4 patients (10%) had vomiting after carboplatin infusion.

DISCUSSION

Brain metastases represent a serious obstacle in the management of patients with solid tumors[7]. In almost half of patients, the cause of death is attributable to progression of brain disease[8]. About 40-50% of brain metastases originate from primary cancers in the lung followed by another 15-25% by breast[7]. In our study majority of patients enrolled had primary breast cancer (62%) and 28% had lung cancer.

Radiosensitizers are chemical or pharmacologic agents that enhance the effects of radiation if administered with it. There are many chemicals capable of rendering cells or tissue more sensitive to radiation, but only those agents are clinically useful that enhance tumor cell kill without increasing normal tissue toxicity. Viani et al. in a meta-analysis have shown that WBRT with radiosentizers like ionidamine, metronidazole, misonodazole, motexafin gadolinium, efaproxiral, thalidomide have not improved significatively the overall survival, local control and tumor response compared to WBRT alone for brain metastases[9].

Poor blood–brain barrier (BBB) penetrability of many systemically active chemotherapeutic drugs has been the major limiting factor in exploring the role of chemotherapy in treatment of brain metastases besides the tendency of many patients having had multiple courses of chemotherapy before developing brain metastases and historical exclusion of such patients from clinical trials testing new drugs[7]. BBB is a selective barrier formed by specialized capillary endothelial cells together with pericytes and astrocytic perivascular end feet[10]. Presence of tight junctions between cells create a physical barrier for many large hydrophilic molecules including many chemotherapeutic agents. Furthermore, high levels of drug efflux pumps are expressed on BBB which actively remove chemotherapy drugs from the brain[11]. Although BBB becomes compromised as metastatic lesions grow beyond 1-2 mm in size, this disruption of BBB may not be homogenous and it might remain intact in parts of tumor. In addition, there are likely micro-metastatic deposits in many patients at time of diagnosis, that have intact BBB[11]. Therefore, treatment options overcoming the challenge of an intact BBB are needed for improved intracranial disease control.

Table-1: Characteristics of patients undergoing whole brain radiotherapy with carboplatin.

Parameter	n(%)
Sex	
Male	13(31)
Female	29(69)
Age	
20-30years	04(10)
31-40years	10(24)
41-50years	12(28)
51-60years	10(24)
61-70years	06(14)
Primary tumor site	
Breast	26(62)
Lung	12(28)
Colorectum	01(2.4)
Sarcoma	01(2.4)
Renal cell carcinoma	01(2.4)
Germ cell tumor	01(2.4)

Carboplatin is a platinum analog chemotherapy drug which is cell cycle- phase nonspecific agent. It acts by formation of DNA adducts resulting in inhibition of DNA synthesis and function as well as inhibition of transcription. It is widely distributed in body tissues, crosses BBB and enters the cerebrospinal fluid (CSF). It is a radiosensitizing agent and has activity against many tumors especially lung, breast, bladder and testicular cancers[6]. Different doses of carboplatin have been used by different researchers, ranging from 70 mg/m^2 daily with WBRT of 5 days to 35

mg/m²/dose for 30 doses with craniospinal radiation[12,13]. We chose 150 mg/m² weekly for two weeks making total dose of carboplatin over time almost equal to the recommended phase II dose found by Jakachi et al[13].

In 2004 Guerrieri et al. used WBRT with concomitant carboplatin for patients with brain metastases from NSCLC for the first time. It was a multi-institutional, randomized controlled trial (RCT) with overall survival as the primary endpoint. The trial was terminated early due to low patient accrual, thus limiting the ability to draw statistically significant conclusions[12]. In a phase 2 study by Antonadou et al WBRT with temozolamide in 24 patients did not show a survival improvement with the addition of temozolomide chemotherapy, but showed a statistically significant improvement in response rates (objective response rate 96%) and an improvement in neurologic function[14]. Temozolamide with WBRT was also used by Verger et al but showed an objective response rate of only 32% in 41 patients with no difference in response rate to patients receiving WBRT alone[15]. Kim et al. in a non-randomized retrospective cohort study of 63 patients showed a survival improvement with the addition of various platinum-based doublet chemotherapies in addition to WBRT in patients of non-small cell lung cancer with brain metastases[16]. These studies lack clear and robust benefit with addition of chemotherapy to WBRT but showed enhanced response rates, specifically in NSCLC with the addition of chemotherapy to WBRT[17].

Our study is a phase-2 prospective trial. Its limitations include no comparison group for patients receiving WBRT alone. We did not assess over-all survival of patients mainly because of poor long term follow up of our patients and heterogeneity in terms of disease control at extra cranial sites and previous treatments received by patients. Within its limitations it showed statistically significant improvement in ECOG PS of patients and an objective response rate of 86% compared to 60% in historic control of WBRT alone[4]. The radiological response was most striking in patients with lung cancer, none of the patient showing SD or PD and 67% showing CR. Poor response rate was observed in patients having disease refractory to chemoradiotherapy like renal cell carcinoma and sarcomas. The treatment was well tolerated and no grade 3/4 toxicity was observed in any patients.

In future large scale RCTs are needed to further evaluate role of carboplatin and other chemotherapeutic/molecular targeted therapies with WBRT. Optimal dosing schedules of both chemotherapy and radiotherapy, sequencing of different modalities and effect on over-all survival are yet to be discovered.

CONCLUSION

With its limitation, the results of our study has shown that WBRT with carboplatin as radiation sensitizer is effective in palliation of patients with metastatic brain disease. Further large scale RCTs are needed to make changes in routine clinical practice.

REFERENCES

1. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neurooncol.2005; 75(1):5–14
2. Asghar AH, Mahmood H , Faheem M, Rizvi S, Sajid A, Irfan J. Therapeutic effects of 20 Gray Radiotherapy over a week in the management of brain metastases. J Pak Med Assoc 2009; 59:278-81
3. Eichler AF, Loeffler JS. Multidisciplinary Management of Brain Metastases. Oncologist 2007; 12;884-98.
4. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 2006; 24:1295–1304.
5. Tsao MN, Lloyd N, Wong R, Chow E, Rakovitch E, Laperriere N. Whole brain radiotherapy for the treatment of multiple brain metastases. Cochrane Database Syst Rev 2006; 3:CD003869.
6. Chu E, Obermiller A, Harrold LJ, Tiedemann D, Copur MS. Chemotherapeutic and biologic drugs. In: Chu E, DeVita VT Jr, eds. Physicians Cancer chemotherapy drug manual 2012. Jones & Bartlett learning, Burlington 2012; 69-72.
7. Eichler AF, Chung E, Kodack DP, Loeffler JS, Fukumura D, Jain RK. The biology of brain metastases—translation to new therapies. Nat Rev Clin Oncol 2011; 8(6): 344–356.
8. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322:494–500.
9. Viani GA, Manta GB, Fonseca EC, De fendi LI, Afonso SL, Stefano EJ. Whole brain radiotherapy with radiosensitizer for brain metastases. J Exp Clin Cancer Res 2009; 28:1.
10. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006; 7:41–53.
11. Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in mouse brain metastases of breast cancer. Clin Cancer Res. 2010; 16:5664–5678.
12. Guerrieri M, Wong K, Ryan G, Millward M, Quong G, Ball DL. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. Lung Cancer 2004; 46(1):107–111.

13. Jakacki RI, Burger PC, Zhou T, Holmes EJ, Kocak M, Onar A et al. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol. 2012; 30(21):2648-53.
14. Antonadou D, Paraskevaidis M, Sarris G, Coliarakis N, Econo-mou I, Karageorgis P et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. J Clin Oncol 2002; 20(17):3644–3650.
15. Verger E, Gil M, Yaya R, Vinolas N, Villa S, Pujol T et al. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. Int J Radiat Oncol Biol Phys 2005; 61(1):185–191.
16. Kim DY, Lee KW, Yun T, Kim DW, Kim TY, Heo DS et al. Efficacy of platinum-based chemotherapy after cranial radiation in patients with brain metastasis from non-small cell lung cancer. Oncol Rep 2005; 14(1):207–211.
17. Mehta MP, Paleologos NA, Mikkelsen T, Robinson PD, Ammirati M, Andrews DW et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:71–83.

.....