"The Effect of Simvastatin on The Clinical Outcome of Patients with Brain Metastases Treated with Radiation Therapy: a Pilot Study"

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بسم الله الرحمن الرحيم

"قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ"

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List of abbreviations

ACCP	**The American College of Clinical Pharmacy**
ADL	**Activities of daily living**
AEDs	**Antiepileptic drugs**
ALT	**Alanine transaminase**
AST	**Aspartate transaminase**
AMPK	**Adenosine monophosphate activated protein kinase**
BBB	**Blood brain barrier**
BM	**Brain metastases**
BSA	**bovine serum albumin**
CDK	**Cyclin dependent kinase**
CNS	**Central nervous system**
CR	**Complete response**
CSC	**Cancer stem cells**
CT	**Computed tomography**
CYP 450	**Cytochrome P 450**
ECM	**Extra cellular matrix**
ELISA	**Enzyme-linked immunosorbent assay**
e-NOS	**Endothelial nitric oxide synthase**
EORTC QLQ-C30	**European Organization for Research and Treatment of Cancer quality of life questionnaire-core 30**
GGPP	**Geranylgeranyl diphosphate**
HDL	**High density lipoprotein**
HMG CoA	**Hydroxyl methyl glutaryle co-enzyme A**
HRP	**Horseradish peroxidase**
HRQL	**Health related quality of life**
IBC	**Inflammatory breast cancer**
IL	**Interleukin**
KPS	**Karnofsky performance status**
LDL	**Low density lipoprotein**
LMWHs	**Low molecular weight heparins**

MGd	**motexafin gadolinium**
MMSE	**Mini mental state examination**
MoCA	**Montreal cognition assessment**
MRI	**Magnetic resonance imaging**
NE	**not evaluated**
NF-kB	**Nuclear factor kappa B**
OS	**Overall survival**
PD	**Progressive disease**
PFS	**Progression free survival**
PMRT	**Postmastectomy radiation therapy**
PR	**Partial response**
QOL	**Quality of life**
RECIST	**The Revised Response Evaluation Criteria In Solid Tumors**
RPA	**Recursive Partitioning Analysis**
RT	**Radiation therapy**
SD	**Stable disease**
SRS	**Stereotactic radiosurgery**
TMP	**Tetramethybenzidine**
TNF	**tumor necrosing factor**
UNL	**Upper normal level**
VEGF	**Vascular endothelial growth factor**
VTE	**Venous thromboembolism**
WBRT	**Whole brain radiation therapy**

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Abstract

Abstract

Introduction:

Brain metastases (BM) are the most common intracranial tumors in adult and are considered one of the most feared complication of cancer. The management of BM encompasses combination of definitive and supportive treatment. Definitive treatment options are surgery, stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT). Whole brain radiation therapy is indicated for most patients due to the presence of multiple brain lesions, extracranial metastases or other comorbidities that make surgery and SRS not suitable. Whole brain radiation therapy only extends patients survival from 1-2 months to 6-8 months compared to the use of supportive treatment only. Hence, there have been increasing efforts to develop strategies to enhance the efficacy of WBRT without adding additional toxicity to normal tissue. Preclinical studies have shown that statins might have a radiosensitizing radioprotective effect that may enhance BM treatment.

Aim of the work:

The current study was designed to evaluate the effect of simvastatin addition to WBRT on the clinical outcome of patients with BM.

Patients and methods:

The study was carried out, at the Clinical Oncology Department- Ain Shams University Hospitals, on 50 Egyptian cancer patients with BM who were randomized to one of the two groups: Control group received WBRT 30 Gy (divided on 10 fractions, 5 fractions/week), and Simvastatin group received the same regimen of WBRT in addition to simvastatin 80 mg once daily for the radiation therapy period.

The study objectives were evaluation of radiological response at 4-weeks after WBRT, 1-year progression free survival (PFS) and 1-year overall survival (OS), in addition to evaluation of the following parameters at baseline, after WBRT and 4-weeks after WBRT; neurocognitive function assessment using Montreal cognition assessment (MoCA) test and quality of life (QOL) assessment using Katz index of independence in activities of daily living and health related quality of life (HRQL) questionnaire EORTC QLQ-C30 and its brain module BN20. Safety evaluation included myopathy

assessment, liver function tests evaluation at baseline and after WBRT and assessment of WBRT toxicity profile. Baseline and after WBRT levels of serum S100B protein, a potential prognostic marker of brain injury, were also evaluated.

Results:

The current study has shown that there were non-significant differences between the two arms with respect to radiological response, 1-year PFS and 1-year OS. At baseline, all patients had cognition impairment (MoCA score < 26). Non-significant differences were found between groups and within group with respect to baseline, after WBRT and 4-weeks after WBRT scores of MoCA.

Regarding patients' QOL, non-significant changes were found between the two groups and within group regarding Katz index scores at baseline, after WBRT and 4-weeks after WBRT. The HRQL questionnaires' results have shown that there were non-significant differences between groups and within group except with the hair loss scale that showed significant deterioration at 4-weeks after WBRT in both arms.

The addition of simvastatin was tolerated with no added or unexpected toxicity. There was no significant difference at baseline among the two groups and the healthy control regarding serum S100B protein and the comparisons of baseline and after WBRT between groups showed non-significant changes.

Conclusion:

The addition of simvastatin 80 mg once daily to WBRT was tolerated but it has not improved the clinical outcomes of patients with BM.

Key words:

Simvastatin – Brain metastases – Whole brain radiation therapy – Quality of life – S100B protein.

Review of literature

Brain metastases (BM)

Brain tumors are classified into; primary brain tumors**,** that arise from cells native to the central nervous system (CNS) and originate in the brain itself, and metastatic brain tumors, that originate from tissues outside the CNS and then spread secondarily to the brain **(Patchell, 2003)**.

Brain metastases are the most frequent intracranial tumors in adults and are considered one of the most feared complications of cancer, because they often cause incapacitating neurologic symptoms. In addition, surgical resection, a major treatment option in other types of cancers, is not suitable for many patients with BM and also can cause neurologic morbidity **(Lassman and DeAngelis, 2003).**

Epidemiology:

I- Incidence

The exact incidence of BM is still unknown due to several factors:

a) Cancer databases are often incomplete and brain imaging is not routinely performed on neurologically asymptomatic cancer patients leading to underestimation of the incidence of BM **(Gavrilovic and Posner, 2005).**

b) All studies on the incidence of BM have methodological limitations related to insensitivity or inaccuracy of data collection and differences in diagnosis practices, referral patterns, health care access, populations selection **(Stelzer, 2013).**

A summary of the previous population based studies is represented in table (1) **(Fox et al., 2011).** However, these studies are relatively old and they predate the newer chemotherapies available for cancer management and the use of advanced imaging technology for diagnosis **(Nayak et al., 2012)**.