Prospective Comparative Study Between Concurrent Temozolamide With Radiation Therapy Versus Concurrent Treatment Followed By Adjuvant Temozolamide In Glioblastoma Multiforme

Submitted for fulfillment of the M.D. Degree in

CLINICAL ONCOLOGY

By

Ehab Saad Abdel Naby

MSc. Faculty of medicine -Cairo University

Under The Supervision of

Prof. Dr. Magda Moustafa

Professor of Clinical Oncology,
Faculty of Medicine, Cairo University

Prof. Dr. Eman Abdel Hady

Professor of Clinical Oncology,
Faculty of Medicine, Cairo University

Prof. Dr. Amr Mohamed Amin

Professor of Nuclear Medicine,
Faculty of Medicine Cairo University

Dr. Ashraf Monir

Lecturer of clinical oncology
Faculty of medicine Cairo University

Department of Clinical Oncology& Nuclear Medicine

Faculty of medicine

Cairo University

(NEMROCK)

2014

بسم الله الرحمن الرحيم

Acknowledgment

I would like to start this humble work by expressing my deepest gratitude to Allah and all the team that helped me in achieving it.

I wish to thank my **Prof. Dr. Magda Moustafa**; who honored me by carrying out the burden of meticulously revising my script and guiding my thoughts.

I am also profoundly grateful to **Prof. Dr. Eman Abdel Hady**, for her nice guidance and enormous support that was a great help to me.

I am deeply indebted to **Prof. Dr. Amr Mohamed Amin**, for his great support and encouragement.

I am also thankful to my dear guide, **Dr. Ashraf Monir**, for his patience and support in building this thesis step by step.

Many thanks go to **Prof. Dr. Samy El Serafi** for his great help to complete the work throughout this thesis.

I would like to thank all members of the Department of Clinical Oncology, Faculty of Medicine, Cairo University; NEMROCK for their help.

Last, but not least, I would like to give my special thanks to my parents and my wife for their support.

Abstract

The benefit of radiotherapy alone, in inoperable patients, or in combination with surgery, has been demonstrated in several phase III trials. In order to improve the outcome, multiple combinations of surgery, radiotherapy and chemotherapy have been evaluated in several studies there are ongoing trials to evaluate combination of TMZ with other chemotherapeutic drugs and targeted agents in the term of response rate, median survival and progression free survival hoping to improve the outcome in patients with glioblastoma multiforme.Our study was designed to randomize patients either to receive the standard treatment including radiotherapy concomitant with TMZ followed by 6 months of adjuvant TMZ versus radiotherapy concomitant with TMZ followed by observation, aiming at minimizing the cost of the treatment without interfering with the benefit of the patient and also avoiding the adjuvant treatment related toxicity.

Keyword

Glioblastoma- TEMOZOLAMIDE- DMSA-TMZ

List of contents

List of figures

List of tables

List of abbreviations

AA: Anaplastic astrocytoma

ALA: Aminolevulinic acid

ASCO: American Society of Clinical Oncology

ATRA: All-trans retinoic acid

BTCG: Brain Tumor Cooperative Group

BTSG: Brain Tumor Study Group

CBTRUS: Central Brain Tumor Registry of the United States

CDKN: Cyclin dependant kinase

CED: Convection-enhanced delivery

CI: Confidence interval

CNS: Central nervous system

CRT: Conformal radiotherapy

CSF: Cerebrospinal fluid

CT: Computed tomography

DFMO: D,L-alpha-difluoromethylornithine

DNA: Deoxyribonucleic acid

DVH: Dose-volume histogram

EGFR: Epidermal growth factor receptor

EGFRvIII: Epidermal growth factor receptor variant III

EORTC: European Organization for Research on Treatment of Cancer

FDG-PET: Fluorodeoxyglucose-Positron emission tomography

FISH: Fluorescence in situ hybridization

FSRT: Fractionated stereotactic radiotherapy

GBM: Glioblastoma multiforme

GTV: Gross tumor volume

HDT: High-dose chemotherapy

HGF: Hepatocyte Growth Factor

HIF: Hypoxia-inducible factor

HR: Hazard ratio

IA: Intra-arterial

ICP: Intracranial pressure

IDH1: Isocitrate dehydrogenases-1

IFNa: Interferon alpha

IFNb: Interferon beta

IFRT: Involved field radiation therapy

IL: Interleukin

IMRT: Intensity-modulated radiotherapy

KPS: Karnofsky performance status

LDR: Low-dose rate

MET-PET: Methionine-Positron emission tomography

MGMT: Methylguanine-DNA methyltransferase

MIBI: Methoxyisobutylisonitrile

MMR: Mismatch repair

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

1H MRS: Proton magnetic resonance spectroscopy

NF1: Neurofibromatosis type 1

O6-BG: O6-benzylguanine

PDGF: Platelet-derived growth factor

PET: Positron emission tomography

PFS: Progression free survival

PNETs: Primitive neuroectodermal tumors

PTV: Planning target volume

RB: Retinoblastoma

RPA: Recursive partitioning analysis

RT: Radiation therapy

RTOG: Radiation Therapy Oncology Group

RTPCR: Reverse transcriptase polymerase chain reaction

SPECT: Single photon emission CT

SRS: Stereotactic radiosurgery

SRT: Stereotactic radiotherapy

Tc-99m (V) DMSA: Pentavalent Tc-99m dimercaptosuccinic acid

TD: Tolerance dose

TGF: Transforming growth factor

TKs: Tyrosine kinases

Tl (201): Thallium-201

TMZ: Temozolomide

TTF: Tumor Treating Fields

VEGF: Vascular endothelial growth factor

VEGF: Vascular endothelial growth factor

VHL: von Hippel-Lindau

WBRT: Whole brain radiation therapy

WHO: World Health Organization

Introduction

The malignant gliomas are rapidly progressive brain tumors that are divided into anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) and glioblastoma multiforme (GBM) based upon their histopathologic features. **(Wen et al., 2008).**

Glioblastoma multiforme is best managed with a combined modality approach, incorporating maximal surgical resection, adjuvant postoperative radiation therapy, and adjuvant chemotherapy. **(Laws et al., 2003).**

Different treatment modalities of glioblastoma multiforme include :- 1) Surgery which is associated with improved overall survival rates and clinical outcomes. 2) Radiotherapy which significantly improved survival over supportive care alone or with chemotherapy. 3) Chemotherapy which failed to demonstrate a clear benefit when used as adjuvant treatment alone in several randomised trials. **(Bohan et al., 2004).**

The most important prognostic factors affecting the response to postoperative treatment are age, tumor grade (anaplastic glioma versus GBM), the extent of initial surgical resection and Karnofsky performance status (KPS). **(Gorlia et al., 2008).**

Temozolomide, an oral alkylating agent, is the preferred agent for adjuvant chemotherapy in patients with malignant gliomas. The preclinical studies have revealed its good oral bioavailability, anti-tumor activity and ability in penetrating the blood brain barrier. **(Stupp et al., 2009).**

In the late1990's, TMZ seemed promising for the treatment of recurrent GBM **(Newlands et al., 1997, Brock et al., 1998).** A pilot phase II study showed that concomitant TMZ with conventionally fractionated radiotherapy, followed by six cycles of the drug as adjuvant therapy was feasible. **(Stupp et al., 2002)**

The benefit of using temozolomide concurrently with radiation followed by adjuvant temozolomide compared with radiation alone was demonstrated in a phase III trial of 573 people who underwent surgery for glioblastoma. Compared to people who had radiation alone, temozolomide improved overall survival at two years (10 versus 26 percent, respectively). **(Stupp et al., 2005).**

One question arising is the contribution of the concomitant and the adjuvant drug doses which is now being investigated in the ongoing EORTC-Intergroup trial on high grade glioma (CATNON Intergroup trial, started in 2011).

Aim of work

The primary purpose of the study is to compare the efficacy and toxicity of Temozolamide when given as adjuvant treatment for 6 months after its concurrent treatment with radiotherapy versus Temozolamide concurrently with radiotherapy alone in patients with glioblastoma multiforme.

Primary outcome parameters:

1- Progression-free survival

2- Radiological tumor response

Secondary outcome parameters:

1- Overall survival

2- Toxicity of treatment in both treatment arms

3- One of the aims of our work is to investigate the role of pentavalent technetium-99m-dimercaptosuccinic acid [Tc-99m (V) DMSA] brain SPECT in assessment of disease response and its prognostic value with survival in patients with glioblastoma multiforme.

REVIEW OF LITERATURE