

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

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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

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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 late 1990'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