Recent Modalities in the Management of High Grade Glioma

Essay

Submitted for partial fulfillment of master degree in Clinical Oncology and Nuclear Medicine

By

Nahla Mohmed Negm

M.B.B.Ch

Under Supervision of

Prof. Dr. Eman Mohmed Tawfiek El Shiekh

Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

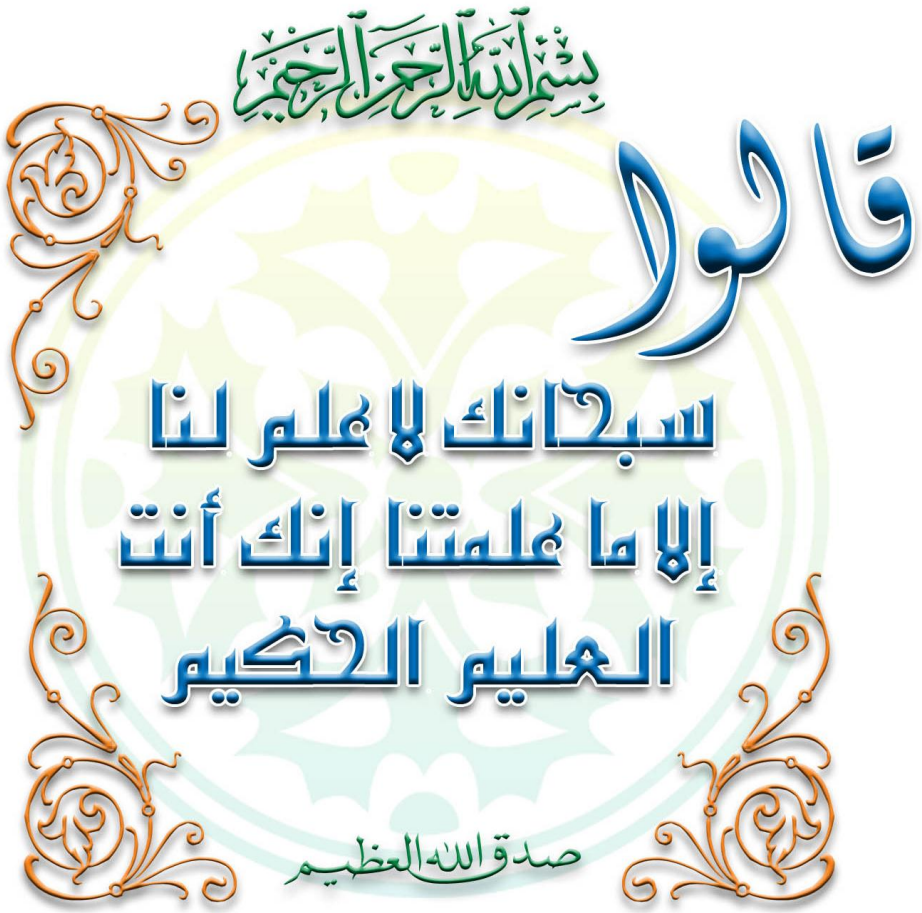
Dr. Waleed Abd El Monem Biomy

Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Dr. Ramy Refaat Youseef Ghali

Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2013



سورة البقرة الآية: ٣٢

Acknowledgement

First, I wish to express my deep thanks, sincere gratitude to

ALLAH

who always helps me, care for me and grunted me the ability to accomplish this thesis. I would like to express my deepest gratitude, thanks and gratefulness to ***Prof. Dr. Eman Mohmed Tawfiek El Shiekh****, Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine – Ain Shams University, for her enthusiastic support, encouragement valuable scientific advices, and great help through out of the accomplishment of this work. May God bless her.*

My sincere thanks to ***Dr. Waleed Abd El Monem Biomy****, Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine – Ain Shams University, for his kind and meticulous supervision, support, help, valuable supervision all through the work.*

Many thanks, and sincere gratitude to ***Dr. Ramy Refaat Youseef Ghali,*** *Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine - Ain Shams University, for his kind supervision encouragement and meticulous revision of this work.*

Words can never express my sincere thanks to ***my parents and my sisters*** *for their generous support and continuous encouragement.*

I would like to express my overlasting gratitude to all ***my dear professors colleagues and friends*** *and all who offered me any kind of help, encouragement wishing them the best of all.*

Nahla Mohmed Negm

List of Contents

List of Abbreviations

Abb.	Meaning
18 F-FDG PET	18 fluorine-fluorodeoxy glucose positron emission tomography
3DCRT	Three-dimensional conformal radiation
5-ALA	5-Aminolevulinic acid
AA	Anaplastic astrocytoma
ADP	Adenosine diphosphate
AED	Antiepileptic drug
ALL	Acute lymphoplastic leukemia
AO III	Anaplastic oligodendrogliomas
BBB	Blood brain barrier
BCNU	Bis-chloroethyl nitrosourea
BMP	Bone morphogenic protein
BNCT	Boron neutron capture therapy
BUD	Rbromo deoxy uridine
CBF	Cerebral blood flow
CBTRUS	Central Brain Tumor Registry of the United States
CBV	Cerebral blood volume
CCNU	Lomustine
CHK1&CHK2	Checkpoint kinases
CNS	Central Nervous System
CSF	Cerebrospinal fluid
CT	Computed Tomography
CTV	Clinical tumor volume
DNA	Deoxyribonucleic acid

Abb.	Meaning
DTI	Diffusion tensor magnetic resonance imaging
EBRT	External Beam Radiation Therapy
EGFR	Epidermal growth factor receptor
FDG	Fluoro-2-deoxy-d-glucose
FLT-1	Fms-related tyrosine kinase 1
FMRI	Functional MRI
FSRT	Fractionated stereotactic radiotherapy
GBM	Glioblastoma multiforme
Gd	Gadolinium
GFAP	Glial fibrillary acidic protein
GTV	Gross tumor volume
HGF	Hepatocyte growth factor
HGG	High grade gliomas
HSF	Hepatocyte scatter factor
HSV-1	Herpes simplex virus type 1
ICP	Intra-cranial pressure
IDH1	Isocitrate dehydrogenase 1
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
KDR	Kinase insert domain receptor
LET	Linear energy transfer
MAP	Microtubule-associated protein
MDPD	Maximum dose/prescription dose
MG	Malignant gliomas
MGD	Motexafin gadolinium
MGMT	Methyl guanine methyl transferase

Abb.	Meaning
MLC	Multi-leaf collimator
MPG	Methyl purine glycosylase
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MRS	Magnetic resonant spectroscopy
NCI	National cancer institute
NCIC	National Cancer Institute of Canada
NF1	Neurofibromatosis type 1
NSCs	Neural stem cells
O6-BG	O6-benzyl guanine
OAR	Organs at risk
OPCs	Oligodendrocyte progenitor cells
OVs	Oncolytic viruses
PCT	Perfusion computed tomography
PCV	Procarbazine, lomustine (CCNU), and vincristine
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGFR-α	α Platelet-derived growth factor receptor-α
PET	Positron emission tomography
PI3	Phosphoinositide-3
PP	Pseudo progression
PTEN	Phosphatase and tensin homolog
PTV	Planning target volume
QOL	Quality of life
RAS	Rat sarcoma
RN	Radiation necrosis

Abb.	Meaning
RSP	Relative survival percentages
RTOG	Radiation therapy oncology group
SEER	Surveillance epidemiology and end results
SPARC	Secreted protein acidic and rich in cysteine
SPECT	Single photon emission computed tomography
SRS	Stereotactic radiosurgery
SS	Step-and-shoot
STAT3	Transcription-3
SVZ	Sub ventricular zone
TGF- α	α transforming growth factor-α
TMZ	Temozolomide
TSP1 &TSP2	Thrombospondins 1 and 2
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau syndrome
VMAT	Volumetric-modulated arc therapy
VPF	Vascular permeability factor
WHO	World Health Organization

List of Tables

List of Figures

Introduction

Primary brain tumors are uncommon and comprise only 1.6% of cancers. Gliomas constitute 40 per cent of all primary Central Nerves System (CNS) tumors. They arise from glial cells and are classified by cell type into astrocytomas, ependymoma and oligodendroglioma. High grade gliomas now account for nearly 80% of malignant brain tumors. Glioblastoma (GBM) is the most common brain tumor **(Fisher et al., 2007).**

Men are more commonly affected than women. The peak incidence occurs in the age range of 65 to 75 years, and the median survival time is inversely proportional to age; these findings have prompted a redoubling of efforts in elderly subpopulations **(Grossman et al., 2004).**

Most gliomas are sporadic, but genetic susceptibility is suspected based on the occurrence of multiple brain tumors in families with germline mutation of the TP53 suppressor gene and patients with neurofibromatosis type I as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome contributes to less than 5% of GBMs **(Farrell and Plotkin, 2007).**

Generally patients present with combinations of headaches, nausea, and vomiting, neurologic manifestations, disturbed conscious level (DCL) depending on tumor size and location **(Fine et al., 2005).**

Magnetic resonance imaging (MRI) is the modality of choice for diagnosis and evaluation of intracranial neoplasms. Computed topography (CT) and magnetic resonance spectroscopy (MRS) might be used for diagnosis also **(Henson et al., 2005).**

Patients with malignant gliomas require a tissue diagnosis in order to guide further clinical management. This tissue diagnosis can be obtained during craniotomy where the goal is the safe removal of the largest possible volume of tumor to establish a diagnosis and relieve mass effect **(Stummer et al., 2006).**

Postoperative radiotherapy extends median survival to 9-12 months. The standard of care is (60 Gy, 30-33 fractions of 1.8-2 Gy) **(Laperriere et al., 2002; Stupp et al., 2009).** There are now multiple techniques like Intensity-modulated radiotherapy (IMRT) **(Narayana et al., 2006)**.

Concomitant chemo-radiotherapy by Temozolamide (75 mg/m2) administered daily (1-1.5)hours before radiotherapy,

followed by 6 adjuvant cycles of Temozolamide (150-200 mg/m2) daily x5 schedule every 28 days, improved the median survival for the combination treatment arm (14.6 vs12.1 months) as well as a significant increase in 2-year survival (26% vs 10%) **(Stupp et al., 2005; Stupp et al., 2009).**

Some studies suggest that the key may lie in identifying the patients most likely to respond based on molecular profiling of tumor tissue **(Ahluwalia and Gladson, 2010).** An exception is the use of agents that target vascular endothelial growth factor (VEGF) or VEGF receptors (VEGF) is Bevacizumab, a monoclonal antibody against VEGF, is the most widely studied of these antiangiogenic strategies **(Friedman et al., 2009)**.

The development of BV as a treatment option for recurrent GBM has raised the possibility that first-line treatment of newly diagnosed GBM with BV may be more advantageous than deferring BV until recurrence **(Lai et al., 2008)**. The potential toxicity, as well as the fear of inducing a more invasive tumor phenotype, also tempers enthusiasm until randomized data become available **(Chinot et al., 2011).**

Other antiangiogenic approaches with the anti-integrin cilengitide (CENTRIC) and other agents such as the VEGFR tyrosine kinase inhibitor cedirinib **(Batchelor et al., 2007; Wedge et al., 2004)** are currently addressing this issue (RTOG

0837), also vatalanib (PTK787) an oral pan-VEGRFR tyrosine kinase inhibitor is under study combined with temozolamide for patients with recurrent glioblastoma **(Reardon et al., 2004).**

Immunotherapy generates a vaccine effect through local delivery of an adenoviral vector containing the herpes simplex virus thymidine kinase gene (AdV-tk), followed by an anti-herpetic prodrug. This approach kills tumor cells via necrosis and apoptosis, elicits danger signals, and stimulates antitumor T-cell proliferation. A phase II trial to further evaluate safety, MGMT status, and potential efficacy is ongoing **(Chiocca et al., 2011).**

The 5-year survival rate from the EORTC-NCIC study of patients with GBM treated with radiotherapy and temozolomide was approximately 10%, and for patients with favorable prognostic factors it approached 30**% (Stupp et al., 2009).** Moreover, a patient who lived more than 20 years following the diagnosis of GBM was described, perhaps the longest documented survivor **(Sperduto et al., 2009)**. The outcome may have stemmed from the fact that he had a favorable molecular profile (e.g., methylated MGMT promoter, PTEN positive, and TP53 positive). Whether this explained the long survival time is unclear. More importantly, these observations prove that one may strive to create and sustain hope for patients diagnosed with high-grade glioma.

Aim of the Work

The aim of this work is to review the recent modalities in the management of high grade glioma.