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Glioblastoma Multiforme : A Brief Review

Himanshu Mishra | Senior Resident, DR RML IMS, Lucknow, U.P., India

Ritusha Mishra | Senior Resident, IMS, BHU, Varanasi, UP, India

ABSTRACT

Glioblastoma Multiforme is most common primary malignant brain tumour in adults. It rapidly infiltrates the surrounding brain tissue, highly lethal and more common in males as compared to females. It might develope as a denovo disease or might be due to conversion of a low grade glioma in to high grade. Vascular proliferation and necrosis are important pathological features. Radiologically, on Magnetic Resonance Imaging it appears as contrast enhancing lesion with peri-tumoural oedema and central necrosis. Age and performance status are most important prognostic factors. Radiotherapy along with concurrent and adjuvant temozolomide after maximum safe surgical resection is considered as standard of care. Even with combined modality approach recurrence is common. Surgical debulking, brachytherapy, reirradiation, chemotherapy are various treatment options in recurrent settings, but none is curative. Prognosis is poor with 5-year survival around 10%.

KEYWORDS | recurrence, radiotherapy, temozolomide

Gliomas are most common malignant brain tumours. Glioblastoma Multiforme (GBM) corresponds to WHO grade IV glioma and is very aggressive in nature. It rapidly and diffusely infiltrates adjacent brain tissue but metastasis outside central nervous system (CNS) is rare. It can occur in any age group, however most commonly it presents in 6th and 7th decade of life. It has more propensity for males as compared to females.

Molecular biology and genetics of glioblastomas are well studied. There are two different genetic pathways which are suggested for development of GBM, one is de novo pathway while other is progression pathway. GBM arising from de novo pathway is primary GBM while from malignant transformation of low –grade glioma is called secondary GBM. At molecular level, amplification of epidermal growth factor receptor (EGFR) is considered to be an important event for genesis of primary GBM. Similarly malignant transformation of low-grade gliomas in to secondary GBM is very much influenced by overexpression of platelet- derived growth factor, fibroblast growth factor-2 and cyclin-dependent kinase-4 along with mutation in p53 gene and loss of Rb gene. PTEN loss is an important factor involved in both the pathways [1].

Several etiological factors (like use of cell-phones, exposure to nitrosamines) have been studied, however role of only genetic predisposition and exposure to ionizing radiations are proven. Currently there is no strategy for screening of the disease. There is also no conclusive evidence that early detection of the disease will lead to improvement in survival.

Histopathological examination should be carried out very carefully because existance of various degree of differentiation is possible in the same specimen. Low-grade gliomas are well differentiated while high grade gliomas like GBM are poorly differentiated. Vascular proliferation and necrosis are hallmark pathological features of GBM. Nuclear atypia and high mitotic activity are other important features.

Clinical features depend not only on the site of the lesion but also on size of the disease and associated oedema. Patient may develope any combination of the following symptoms-headace, nausea, vomiting, hemiparesis, quadriparesis, visual disturbances, seizures, personality changes, hallucinations and many others depending on the involved area of the brain. Age, Karnofsky Performance Status (KPS) are most important prognostic factors in GBM. Extent of resection and duration of neurological symptoms are other prognostic factors.

Magnetic resonance imaging (MRI) is investigation of choice as it is helpful in suggesting pre-operative diagnosis, depicting extent of disease along with peritumoural oedema and generating appropriate radiotherapy (RT) plans [2]. On T -1 weighted sequences the disease appears as ring-enhancing or heterogenously enhancing lesion, which might be associated with central necrosis. T2-weighted fluid attenuation image recovery (FLAIR) are used to properly assess peri-tumoural oedema as it harbours sub-clinical disease. The differential diagnosis includes brain metastasis, central nervous system lymphoma, stroke , demyelination and several infectious and inflammatory conditions. Pre-opeartive- MRI is required for surgery while post-opertive MRI is essential to know the status of residual disease and for RT planning. Post-operative MRI is done either 48 hours before surgery or after 2 weeks of surgey. This is because surgery induced enhancement and oedema usually developes after 48 hours and persists mainly up to 2 weeks. So it is very difficult to identify residual enhancing lesion and associated peritumoural oedema from that surgery induced on MRI images (done during this period of time). Physiological and functional assessment of tumour is not possible with conventional MRI. However, New MRI techniques, such as MR perfusion, MR diffusion and MR spectroscopy (MRS) can provide physiological information about the tumour related to hemodynamics, cellularity and metabolism respectively. These informations could be better used for response assessment following therapy.

Removal of maximum possible disease volume followed by RT along with concurrent and adjuvant temozolamide (TMZ) is standard of care in GBM patients. Complete resection is not always possible in GBM patients because of extensive disease extent.The goals of the surgery are to provide relief from mass effect and to establish diagnosis. In cases where resection is not possible owing to involvement of large areas of brain, biopsy could be done to provide material for diagnosis. Cerebro-spinal fluid (CSF) diversion procedures could also be done in advanced cases if required to decrease intra-cranial tension. Surgery is usually performed by open craniotomy. Newer advancements in neurosurgery like diagnostic ultrasound, ultrasonic tissue aspirators, lasers, cortical mapping, functional imaging and computer-assisted stereotactic laser techniques have helped a lot in more extensive resection of tumour. The extent of resection is important as it influences survival. Results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials involving 645 GBM patients published by Simpson et al has shown median survival of 11.3 months, 10.4

months and 6.6 months with total resection, sub-total resection and biopsy alone respectively [3].

There is substantial evidence in literature suggesting improved survival advantage with adjuvant RT. Brain Tumour Coopearative Group (BTCG) trials 6901 and 7201 have shown significantly improved survival in patients who received 50 to 60 Gy (1.7-2.0 Gy/ #, single #/ day, 5 days/week) external beam radiotherapy (EBRT) to the whole brain either alone or with chemotherapy compared with those who were treated with either resection and supportive care or with chemotherapy alone. The median survival of patients receiving 60 Gy was 2.3 times longer than that observed for non-irradiated patients. Adjuvant RT not only increases survival, it also has been found to be associated with improvement in performance status of patient.

The RT technique in GBM has evolved through ages. Initially patients were treated with whole brain RT. In 1989 a randomized study , BTCG 80-01 trial by Shapiro et al compared whole brain radiotherapy with partial brain irradiation and demonstrated that there was no difference in overall survival and pattern of recurrences between the two arms [4]. Since then partial brain irradiation has become standard of care. Since their introduction, computerized tomography (CT) and MRI has played a very important role in accurate tumour delineation and subsequently in RT planning. The three-dimensional (3D) conformal radiation technique is widely used for partial-brain irradiation in GBM as it can provide adequate tumour coverage and minimum dose to surrounding normal tissues. Co-registration of pre-and post-operative MRI with planning CT is usually done to get the optimal RT target volume. However optimal target volume is a matter of debate in GBM and opinion varies among different cooperative groups. RTOG suggests a two-phase treatment , where the initial clinical target volume (CTV) typically includes postoperative peritumoural edema plus a 2 cm margin to be covered by 44-50 Gy (with 1.8-2Gy/#), followed by a boost field defined as the residual contrast enhancing tumour plus a 2 cm margin up to 60 Gy [5]. However, the European Organization for Research and Treatment of Cancer (EORTC) describes a single-phase treatment pattern with 2–3 cm margin around the enhancing tumour and resection cavity as evaluated by post-operative MRI [6]. RTOG considers peritumoural oedema in initial CTV as it harbours isolated tumour cells while EORTC prefers single phase treatment based on the fact that maximum tumour recurrences occur within 2 cm of contrast enhancing lesion.

Whatever the technique used, total RT dose of 60 Gy with conventional fractionation is recommended. Medical Research Council (MRC) phase III trial has shown inferior survival results with total RT dose less than 60 Gy [7]. Various studies have shown no difference in patterns of relapse or survival with dose escalation above 60 Gy. Many RT treatment strategies (like altered fractionation, brachytherapy boost, stereotactic radiosurgery boost) have been tried in GBM patients but none has demonstrated improvement in survival [8,9,10].

Many chemotherapeutic agents have been tried in GBM patients as adjuvant treatment to improve the outcomes. Historically nitrosoureas, especially carmustine (bis-chloroethyl-nitrosourea [BCNU]) was the most active single agent used and no other drug or drug combination was found more effective than this. At present the most widely used drug is temozolomide which is a derivative of dacarbazine . It is an orally administered prodrug that undergoes hydrolysis to active metabolite monomethyl triazeno imidazole carboximide after absorption. It causes methylation of guanine at the O- 6 and N-7 positions at the deoxyribonucleic acid (DNA). Rapid absorption, ability to cross the blood-brain barrier and minimal delayed myelosuppression are its major advantages over other chemotherapeutic agents. Its role in GBM is established by an EORTC phase III trial conducted by Stupp et al which compared 60 Gy of radiation with or without concurrent temozolomide (at 75 mg/m^2/day) followed by six cycles of adjuvant therapy with temozolomide (at 200 mg/m^2 for 5 days per month). The trial demonstrated that after a median follow-up of 28 months, the median overall survival improved from 12.1 to 14.6 months and the 2-year overall survival improved from 10.4% to 26.5% with the addition of temozolomide therapy. Based on the results of this trial, RT with concurrent and adjuvant temozolomide after maximum safe surgical resection is considered as standard of care in GBM.

O 6-Methylguanine DNA methyltransferase (MGMT) is a DNA-repair enzyme that removes alkyl groups from the O -6 position of guanine in DNA and therefore repairs damage caused by temozolomide. Methylation of promoter region of this enzyme inhibits it, thus enhancing the action of temozolomide. A retrospective analysis by Hegi et al has shown survival benefit in favour of patients having methylated MGMT promoter as compared to those having non- methylated MGMT promoter [11]. Whether dose- intense temozolomide could cause improvement in survival or not, the issue was addressed by a RTOG trial. RTOG conducted a phase III trial comparing standard temozolomide schedule to a dose- intense temozolamide schedule and demonstrated no significant difference in overall and progression- free survival between the two treatment schedules [12].

Apart from chemotherapeutic agents, many targeted agents have been tried in GBM. Bevacizumab is the most promising targeted agent owing to its antiangiogenic property (angiogenesis is a very important feature of GBM) and is widely used in recurrent GBM. Role of tyrosine kinase blockers, inhibitors of *Ras/MAPK* pathways and many other agents is at present current focus of clinical developement and research.

Most of the patients suffer from recurrence in GBM. Palliative debulking, single agent Bevacizumab, local carmustine wafers and reirradiation are different treatment options, however none are curative. Prognosis is poor in GBM; even after standard treatment 5-year survival is only 9.8%.

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