Glioblastoma Multiforme In Elderly Population

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Citation

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Abstract

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain malignancy in the human race. The management of glioblastoma multiforme (GBM) in elderly patients is not well established in English literature. Despite treatment advances, survival of elderly GBM patients is usually < 12 months. Prognostically favorable elderly GBM patients should be included in prospective randomized combined-modality clinical trials. Quality-of-life issues should be strongly considered in this subset of patients. This is the review article looking into the pattern of presentation, treatment, and other related aspects in this subset of patients as management of glioblastoma multiforme (GBM) in elderly patients is not well established.

EPIDEMIOLOGY

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain malignancy. In English literature it accounts for 52% of all brain tumor cases and 20% of all intracranial tumors[1]. Despite being the most prevalent form of primary brain tumor, the incidence is only 2–3 per 100,000 in Europe and North America[2].

ANATOMIC OCCURRENCE

Glioblastoma multiforme occur most often in the subcortical white matter of the cerebrum, but the most frequently affected sites reported are the temporal (31%), parietal (24%), frontal (23%), and occipital (16%) lobes, respectively[3]. Tumor infiltration often extends into the adjacent cortex or the basal ganglia. When a tumor in the frontal cortex spreads across the corpus callosum into the contralateral hemisphere, it creates the appearance of a bilateral symmetric lesion, hence the term butterfly gliomas. Sites for Glioblastoma that are much less common are the brainstem (often found in children), the cerebellum and the spinal cord[4].

CLINICAL PRESENTATION

Glioblastoma multiforme have been reported in all age groups but it affects adults preferentially with a peak incidence at 45-70 years[5]. The most common presentation of patients with glioblastoma is headaches, seizures, slowly progressive neurologic deficit, higher function impairment, or they may present with generalized symptoms of increased intracranial pressure (ICP) such as persistent headaches, nausea and vomiting[6]. Signs and symptoms predominantly depend on the location of mass rather than the pathology.

ETIOLOGY

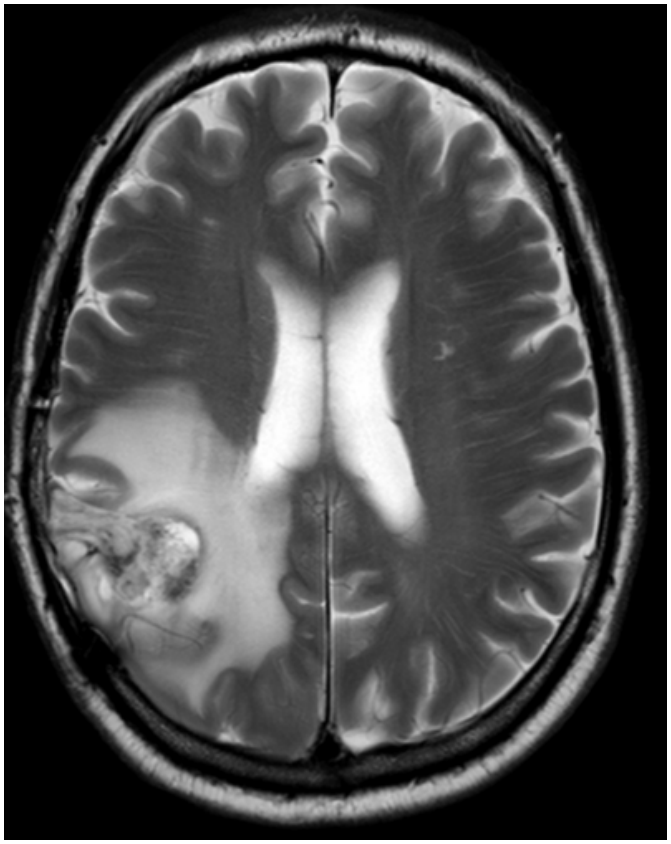
At present, the etiology of glioblastoma is unknown in science of medicine. However familial gliomas have been reported and account for approximately 5% of malignant gliomas. Less than 1% of gliomas are associated with a known genetic syndrome such as Li-Fraumeni syndrome, Turcot syndrome and neurofibromatosis.[7]

DIAGNOSIS

Diagnosis is usually done by imaging which includes CT scan and or MRI scans (Figure 1).

Figure 1

Figure 1: MRI scan showing ring enhancing infiltrating lesion in right parietal-temporal lobe with associated white matter changes most likely reflecting neoplastic mass with vasogenic edema



Positron emission tomography (PET) scans and magnetic resonance (MR) spectroscopy can be helpful to identify glioblastoma in difficult cases, such as those associated with radiation necrosis or hemorrhage. On PET scans, increased regional glucose metabolism closely correlates with cellularity and reduced survival. MR spectroscopy demonstrates an increase in the choline-to-creatine peak ratio, an increased lactate peak, and decreased N-acetylaspartate (NAA) peak in areas with glioblastomas[8]. Electroencephalography (EEG) performed on a patient with glioblastoma multiforme may show generalized diffuse slowing and/or epileptogenic spikes over the area of the tumor. However, no specific findings are pertinent for glioblastoma on EEG examination[9].

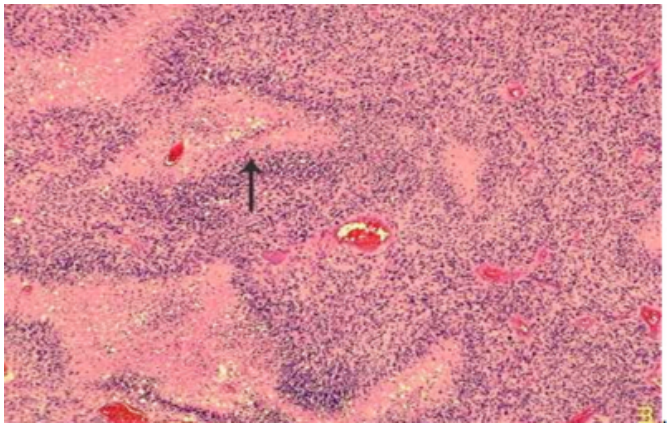
PATHOGENESIS

Macroscopically, glioblastomas are poorly delineated with peripheral grayish tumor cells, central yellowish necrosis and multiple areas of old and recent hemorrhages. Most glioblastomas of the cerebral hemispheres are clearly intraparenchymal with an epicenter in the white matter, but some extend superficially and contact the leptomeninges and dura matter.

Pathologically glioblastoma multiforme tumors are composed of poorly differentiated, pleomorphic astrocytes with marked nuclear atypia and brisk mitotic activity (Figure 2)

Figure 2

Figure 2: Pathology showing microscopic feature of poorly differentiated cells with abundant palisading necrotic foci.



Necrosis is an essential diagnostic feature, and prominent microvascular proliferation is commonly seen[10]. Glial fibrillary acidic protein (GFAP) remains the most valuable marker for malignant astrocytomas. Although immunostaining is variable and tends to decrease with progressive dedifferentiation, many cells remain immunopositive for GFAP even in the most aggressive glioblastomas. Vimentin and fibronectin expression are common but less specific[11].The heterogeneity is remarkable which often makes histopathological diagnosis a serious challenge. Over the past decade, the concept of different genetic pathways leading to the common phenotypic endpoint has gained general acceptance in oncology. Genetically, primary and secondary glioblastomas show little overlap and constitute different disease entities.

MUTATIONS

Studies are beginning to assess the prognoses associated with different mutations[12].Loss of heterozygosity (LOH on chromosome arm 10q) is the most frequent gene alteration for both primary and secondary glioblastomas occurring in 60-90% of cases[13].Mutations in p53, a tumor suppressor gene appears to be deleted or altered in approximately 25-40% of all glioblastoma multiforme[14]. Epidermal growth factor receptor (EGFR) gene is involved in the control of cell proliferation and these tumors typically show a simultaneous

loss of chromosome 10 but rarely a concurrent p53 mutation. Overexpression or activation mutations in this gene are more common in primary glioblastoma, with mutations appearing in 40-50% of these tumors. One such common variant, EGFRvIII has shown promise as a target for kinase inhibitors, immunotoxins, and peptide vaccines[15]. Amplification or overexpression of MDM2 constitutes an alternative mechanism to escape from p53 -regulated control of cell growth by binding to p53 and blunting its activity. Overexpression of MDM2 is the second most common gene mutation in glioblastoma multiforme and is observed in 10-15% of patients. Some studies show that this mutation has been associated with a poor prognosis[16].

TREATMENT

Main modality of treatment is surgical resection. The extent of surgery (biopsy vs. resection) has been shown in a number of studies to affect length of survival. In a study by Ammirati and colleagues (1987), patients with high-grade gliomas who had a gross total resection, had a 2-year survival rate of 19%, while those with a subtotal resection had a 2-year survival rate of 0%.[17] The standard of care till early 2007 was surgical resection to the extent feasible, followed by adjuvant radiotherapy. Dr Stupp in 2007 published their data in which they compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy. A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity[18].

Since the trial, on which modern day practice is based, excluded elderly patients, there is no randomized phase III data to optimize treatment in this subset of patients. Optimal therapy of GBM in the elderly remains an area of controversy. A study conducted in France by Keime-Guibert et al. enrolled total of 81 patients 70 years of age or older with good functional status. Forty-two received comfort care alone, including antiepileptic medication, physical and psychological support, and access to a palliative care team. The other 39 patients received supportive care and radiation therapy (50 Gy in doses of 1.8 Gy per day, given 5 days a week). Patients receiving radiation therapy had a median survival of 29.1 weeks compared with 16.9 weeks for those receiving supportive care alone. Radiation therapy produced a survival benefit regardless of the extent of surgery performed, which ranged from biopsy alone to complete resection. Physical and mental status declined over time in both groups, with no significant differences observed between the groups. Perceived quality of life also did not differ between the groups. The authors stated that, “radiotherapy increases the median survival of elderly patients with glioblastoma who have a good performance status at the start of treatment.” They also noted that, “the optimal dose of radiotherapy in elderly patients remains undetermined.” Other studies have indicated that various other palliative radiation regimens, using different doses and fractionation schemes, may provide similar benefit. However, in recently published papers such a chemoradiotherapy approach in older GBM patients seems to be less effective with higher toxicity rates compared to younger patients. Because Temozolamide (TMZ) may be more toxic in older patients, a personalized pre-treatment test (e.g. the identification of the MGMT promoter methylation status) could be useful to distinguish responders from nonresponder[19]. Dr Roa et al. randomized 100 patients with GBM aged 60 years to receive either hypo fractionated radiotherapy (40 Gy given over 3 weeks) or standard high dose radiotherapy (60 Gy given over 6 weeks). The authors observed no significant difference in overall survival between the two-study groups[20]. The value of combined RT and chemotherapy in the elderly with GBM has now been shown in a small Italian randomized clinical trial reported by Brandes et al. Seventy-nine patients > 65 years old received RT alone, RT plus procarbazine-lomustine-vincristine chemotherapy (median of two cycles per patient), or RT plus temozolomide chemotherapy (median of five cycles per patient). The median survival time and 1-year survival rates were 11.2 months and 32% with RT alone, 12.7 months and 56% with RT + procarbazine-lomustine-vincristine, and 14.9 months and 73% with RT + temozolomide. Survival was significantly better with RT + temozolomide compared to RT alone. Patients with good performance status KPS > 70 had significantly better survival.[21]

In 2010 ASCO, Malmstrom et al presented their data which included the newly diagnosed GBM patients age ≥ 60 years

with performance status of 0-2, randomized to either standard radiation (60 Gy in 2 Gy fractions over 6 weeks) or hypofractionated radiation (34 Gy in 3.4 Gy fractions over 2 weeks) or 6 cycles of chemotherapy with TMZ (200 mg/m^2 day 1-5 every 28 days). Follow-up including quality of life, symptom checklist, and steroid dosing was completed at 6 weeks, 3 months, and 6 months after start of treatment. The primary study end point was overall survival (OS). A total of 342 patients were included. 291 patients were randomized between the 3 treatment options, 51 patients between hypofractionated RT and TMZ. Median age was 70 years (range 60-88), 59% were male and 72% had undergone tumor resection, the remaining 28% had a diagnostic biopsy only. Performance status was 0-1 for 75% of pts. Survival data are available for 334 patients (98%), with 11 patients (3%) being alive. There was no significant difference in OS between the three treatment arms, with median survival being 8 months for TMZ, 7.5 months for hypofractionated RT and 6 months for 6 weeks RT (p=0.14). They concluded that elderly patients with GBM have a short survival. Time-consuming therapy that does not offer longer survival should therefore be avoided. Our study showed no advantage of standard 6 weeks RT compared to hypofractionated RT over 2 weeks or 6 cycles of TMZ chemotherapy. These results indicate that standard RT should no longer be offered to the elderly patient population with GBM. Exclusive TMZ chemotherapy may be an alternative to RT. Subgroup analyses and determination of molecular markers is ongoing. Whether outcome could be improved by concomitant chemoradiotherapy is subject of ongoing clinical trials[22]. Recent studies have shown stereotactic radiosurgery (SRS) has become an effective therapeutic modality for the treatment of patients with glioblastoma multiforme (GBM). It can be utilized as an adjuvant therapy in the management of patients with GBM or added as a boost to external radiation. However whether it will apply to elderly population time will tell as more and more data will be published, but at present seems to be promising[23].

For older patients who are not candidates for a combined modality approach because of poor functional status or significant comorbidity, we suggest shorter courses of radiation therapy, which are more convenient and may offer an advantage because of decreased toxicity. The role of chemotherapy as a monotherapy alternative to RT remains uncertain but has been studied in few phase II studies. Temozolomide has an acceptable tolerance in elderly patients with GBM and KPS less than 70. It is associated with improvement of functional status in 33% of patients and appears to increase survival compared with supportive care alone, especially in patients with methylated MGMT promoter[24].

The development of targeted therapy based on tumor vascular blockade led to the approval of bevacizumab for recurrent or progressive glioblastoma, since it was proven that this offers a new opportunity for patients suffering from this malignancy. Bevacizumab is a recombinant antivascular monoclonal antibody binding to circulating Vascular Endothelial Growth Factor (VEGF) preventing this cytokine from reaching its receptors (VEGFR1 and VEGFR2) on endothelium, resulting in an inhibition of cells proliferation and vessels sprouting. The VEGF family of soluble growth factors consists of five related proteins that have been implicated in angiogenesis (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E), four of which occur in the human genome (VEGF-A, VEGF-B, VEGF-C, VEGF-D)[25]. There are three VEGF receptors (VEGFR1, VEGFR2, and VEGFR3) that play important roles in the angiogenesis of numerous solid malignancies, including glioblastoma. The VEGF family of endothelial growth factors is considered to play a key role in angiogenic processes and has been shown to be secreted by tumor cells and tumor stromal cells (such as macrophages or fibroblasts) .Tumor angiogenic and lymphangiogenic signals are transmitted via three tyrosine kinase cell surface receptors [VEGFR1 (Flt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4)] located on the host vascular endothelial cells, monocytes/macrophages, and hematopoietic precursors[26]. Because VEGF receptors (VEGFRs) are only up-regulated in endothelial cells of newly forming vessels in tumors, a potential target for antitumor therapy will be the VEGFR tyrosine kinases. Inhibition of VEGF-induced angiogenic and lymphangiogenic signals will selectively target the tumor-associated vessels, since cell division of endothelial cells in the normal vasculature is a very rare event. It has been tried in younger population with some success but in elderly population effects are unknown[27]. Radioimmunotherapy has been tried in phase II studies in GBM. With use of anti-epidermal growth factor receptor (125) I-mAb 425 radioimmunotherapy, survival quoted was 15.7 months. The treatment was safe and well tolerated but has not been tested in phase III randomized studies in elderly patient's yet[28].

Recent evidence shows that the incidence of glioblastoma multiforme (GBM) has increased substantially in the elderly population over the past 20 years. For example, some investigators have reported an increase of 5% per year in the

portion of population age ≥ 65 years. Even more dramatic increases (from 30% to 254%) were observed in patient's age ≥ 75 years. Improved diagnostic procedures may be responsible in part for the increased incidence of GBM, but they do not account for all of the changes[29]. So, given the lethal nature of disease and paucity in level-I data, it is very important for oncologist to find out the outcome of our patients who are treated with different approaches. In summary cancer causes disproportionate morbidity and mortality in the geriatric population. A comprehensive assessment in this group can help achieve the required balance between the potential benefits and side effects of therapy.

CONCLUSION

The multidisciplinary approach is highly recommended in treating GBM in elderly population involving neuro-oncologist, neurosurgeon, radiation oncologist, medical oncologist, and palliative care team to optimize the treatment management. Age alone should not be a factor in the decision on which treatment should be given. Treatment should be tailored to match the patient's overall condition, while taking into consideration other aspects such as and his or her wishes. However, more large multicenter study is required to monitor newer agents on brain cancer progression and impact on the elderly population.

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