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Review Article

MANAGEMENT HIGH GRADE GLIOMA IN ELDERLY

Henry Riyanto Sofyan[1,2], Intan Pratiwi, Fahmi Radityamurti[1,3], Anastasia Asylia Dinakrisma,[1,4],Tiara Aninditha[1,2], Irma Savitri[1,2]

[1]Faculty of Medicine, Universitas Indonesia; intan.pratiwi31@ui.ac.id
[2]Departement of Neurology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[3]Departement of Oncology Radiation, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[4]Departement of Internal Medicine, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

Introduction: High-grade glioma (HGG) is an aggressive primary brain tumor with poor prognosis, particularly in elderly patients. Management is complex due to comorbidities, decreased functional status, and increased risk of treatment-related toxicity. Personalized approaches balancing efficacy and quality of life are essential in this population.
Case Report: A 67-year-old male presented with progressive headache, limb weakness, and visual disturbances. MRI revealed a large right temporoparietal lesion suggestive of HGG. Craniotomy and biopsy confirmed a high-grade glioma. The patient had a Karnofsky Performance Status (KPS) of 40, with significant cognitive and functional impairments, along with comorbidities including diabetes and hypertension. Given his frailty, he was treated with hypofractionated radiotherapy and concurrent temozolomide.
Discussion: Treatment decisions in elderly HGG patients should consider age, KPS, cognitive status, and comorbidities. Hypofractionated radiotherapy combined with temozolomide is effective and better tolerated in frail patients. Multidisciplinary care is crucial to manage physical, cognitive, and emotional needs. Cognitive assessment before therapy aids in anticipating treatment impact. Prophylactic treatment for opportunistic infections such as *Pneumocystis jirovecii* is recommended during chemotherapy.
Conclusion: Elderly patients with HGG require individualized, multidisciplinary care. Factors such as performance status, cognitive function, and comorbidities must guide treatment to achieve optimal outcomes while preserving quality of life

Keywords: High-grade glioma, elderly; temozolomide; hypofractionated radiotherapy; frailty; Karnofsky Performance Status; multidisciplinary care; cognitive impairment

INTRODUCTION

High grade glioma (HGG) is a highly aggressive brain tumor with poor prognosis, especially in elderly patients.[1] As an aggressive brain tumor, HGG has a median overall survival (OS) of less than 18 months in general, and less than 12 months in elderly populations.[2] The incidence of HGG peaks in the 60s to 70s age group.[2] Standard treatment includes surgery, radiotherapy, and chemotherapy, but outcomes in elderly patients remain suboptimal. Median survival of glioblastoma is approximately 6.1 months without treatment and 3.2 months in patients older than 70 years.[1]

Elderly patients (≥65 years) with HGG face significantly worse survival outcomes than younger patients. Additionally, those with poor performance status (KPS <60 or ECOG PS >2) also have poorer prognosis. Standard treatment for high-grade glioma (HGG) involves surgery and chemoradiation, but optimal management for elderly or poorly performing patients is debated due to their worse prognosis. These patients often receive less aggressive treatments, though surgery can provide survival and neurological benefits.[3]

Radiation therapy (RT) has shown to improve survival in elderly patients compared to best supportive care (BSC) alone, with similar outcomes for those receiving standard RT (60 Gy/30 fractions) or hypofractionated RT (25–40 Gy in 5–15 daily fractions). Temozolomide (TMZ), an alkylating agent, is effective for patients with O6-methylguanine-

DNA-methyltran sferase (MGMT) gene promoter methylation. A recent phase III trial for GBM patients aged ≥65 years with ECOG PS 0–2 demonstrated improved progression-free survival (PFS) and overall survival (OS) with hypofractionated RT (40 Gy/15 fractions) and concurrent adjuvant TMZ, compared to RT alone, without negatively affecting quality of life (QoL) or functional status.[3] Another agent, mostly used in HGG treatment is dexamethasone. While dexamethasone remains a crucial treatment for managing GBM-associated edema and inflammation, its impact on tumor progression and patient survival raises concerns. The evidence suggests that dexamethasone might be a "double-edged sword," offering short-term symptom relief but potentially worsening long-term outcomes.[4] Patients with HGG are at risk of developing secondary infections, including *Pneumocystis jirovecii* Pneumonia, which may be caused by the disease itself or by the treatments received, such as dexamethasone, temozolomide, and radiation, ultimately affecting the patient's clinical outcome.

Because of the complexity of caring for geriatric patients with high grade glioma (HGG), personalized management of patients with HGG is essential as we strive to balance the effectiveness of treatment with the potential for toxicity, while also considering the various complexities of multiple prognostic factors that

impact expected survival. This paper reports a case of high-grade glioma in a 67-year-old male with a frail condition and its management.

CASE REPORT

A 67-year-old male presents with chronic throbbing headaches that frequently occur at night. One month later, the patient begins to experience heaviness in his legs, starts dragging his feet while walking, and develops visual disturbances. The headaches worsen, accompanied by nausea, vomiting, and increasing weakness in his left leg, accompanied by weakness in his left arm. Brain MRI reveal a lesion that is hypo- to hyperintense on T1, hyperintense on T2 and FLAIR, with intralesional hemorrhage and necrotic areas. There is restricted diffusion on DWI-ADC at the periphery of the lesion, which shows heterogeneous contrast enhancement. The lesion measures approximately 7.8 x 7.8 x 6.4 cm, with surrounding perifocal "finger-like" edema in the periventricular region of the right temporoparietal lobe, left parietal lobe, and the body of the corpus callosum. The MRI findings are suggestive of either a high-grade glioma or metastatic tumor (Figure 1). The patient underwent a craniotomy removal tumor and biopsy. The histological findings are consistent with Adult-type diffuse glioma, NOS, high grade, with a differential diagnosis of Glioblastoma, IDH-wild type, CNS WHO grade 4 and Astrocytoma, IDH-mutant, CNS WHO grade 4. IDH mutation testing is required for further confirmation.

The patient was referred to a third-referral hospital to undergo chemotherapy and radiation. On physical examination, left-sided hemiparesis was observed, with the leg more severely affected than the arm, accompanied by dysarthria due to left hypoglossal nerve paresis.

Before determining the treatment for a patient with high-grade glioma, the patient's functional status needs to be assessed. In this case, we used the Karnofsky Performance Scale (KPS). The patient's KPS score is 40, as the patient is bedridden throughout the day due to the inability to move the left leg. Additionally, the patient requires assistance with eating, personal hygiene, and dressing. Results of his cognitive function assessment were memory impairment (delayed verbal memory), acalculia,

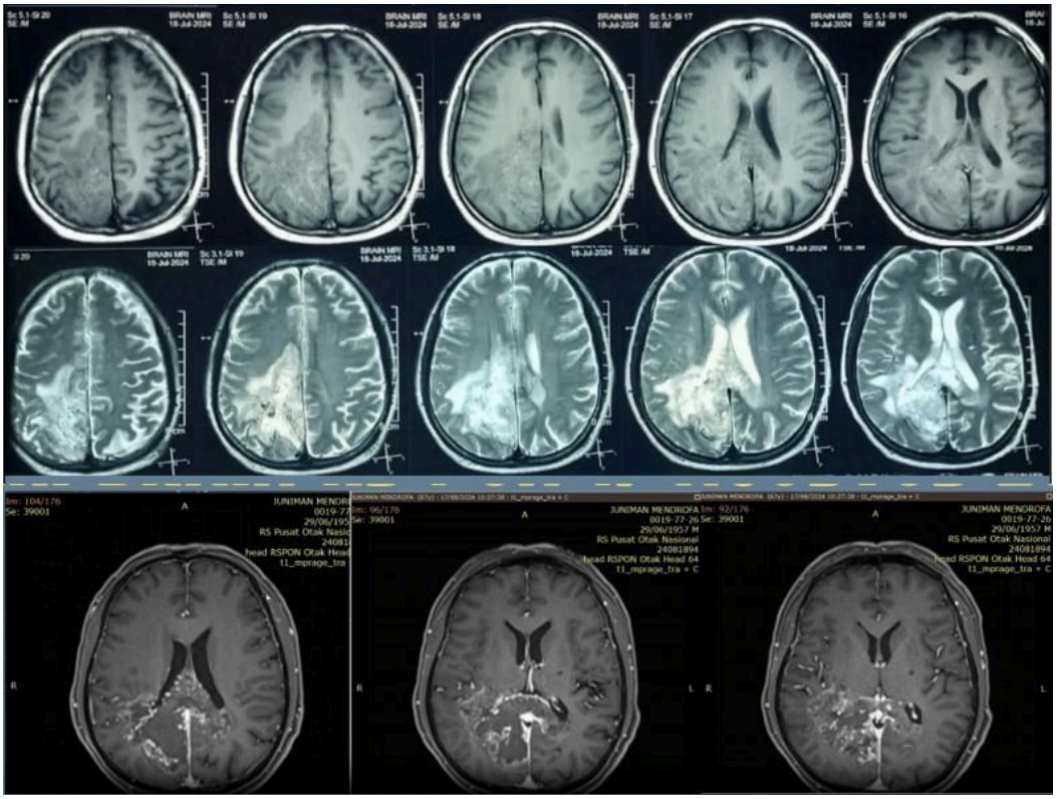

Figure 1. Brain MRI with contrast shows a lesion that is hypo- to hyperintense on T1, hyperintense on T2 and FLAIR, with hemorrhagic components and necrotic areas, accompanied by perifocal edema.

and slowed thought processing. Functional capacity could not be fully assessed due to the patient's visual impairment. The visual impairment may be related to the tumor and peritumoral lesion in the occipital region. The memory impairment may be associated with peritumoral edema in the right hippocampus, while the acalculia may be linked to peritumoral edema in the left parietal region. The slowed thought processing could be related to diffuse lesions and/or generalized peritumoral edema. The patient is a geriatric individual with comorbidities, including type 2 diabetes and hypertension. Based on the Comprehensive Geriatric Assessment (CGA), the patient was found to be independent, with a risk of malnutrition, possible depression, frailty, predictive sarcopenia, and a high risk of falls.

The patient is a frail geriatric. Although the patient is under 70 years old, the Karnofsky Performance Status (KPS) score is < 60. Therefore, the recommended treatment is hypofractionated radiation therapy combined with concurrent temozolomide chemotherapy. During radiation therapy, the patient is managed by a

multidisciplinary team, including specialists in gerontology, psychiatry, medical rehabilitation, internal medicine, and neurology.

DISCUSSION

Gliomas are a diverse group of tumors originating from glial cells in the brain and spinal cord, representing the most common primary brain tumor within the central nervous system[6]. High-grade gliomas are the most aggressive and fast-growing forms of gliomas, categorized as grade 3 (anaplastic astrocytoma and anaplastic oligodendroglioma) and grade 4 (glioblastoma) based on the classification system established by the World Health Organization (WHO)[6,7]. This disease is characterized by a rapid and progressive deterioration of neurological function, which may worsen even during treatment due to its potential toxic effects. High-grade gliomas can cause severe impairment due to physical disabilities, cognitive decline, personality changes, depression, and seizure disorders, necessitating comprehensive multidisciplinary team[8,9]. There are seven principles of care that define what constitutes appropriate and supportive cancer care. The principle are Patient-centred care, Safe and quality care, Multidisciplinary care, Supportive care, Care coordination, Communication, Research and clinical trials. These principles uphold the rights of all patients, as well as the rights of those who care for them and are involved in their journey.[12] Previous studies have identified various prognostic factors, with advanced age and poor functional status consistently associated with lower survival rates. Large population-based research has demonstrated a significant decrease in median survival as age increases, with patients aged 65 and older having a median survival up to six months shorter than younger individuals. In both the original and updated Radiation Therapy Oncology Group recursive partitioning analyses, which categorize prognostic groups for malignant glioma, age over 50 years was found to be the most significant high heterogeneity. A p-value less than 0.05 was considered statistically significant clinical predictor of reduced survival.[1,8] For patients with a newly diagnosed glioblastoma (GBM), the standard treatment consists of

maximal safe surgical resection, followed by radiotherapy combined with concurrent and adjuvant temozolomide chemotherapy.[9] Personalized medicine in high-grade glioma (HGG), particularly glioblastoma (GBM), aims to tailor treatments based on the patient's genetic profile, molecular biomarkers, and overall functional status. This approach improves treatment efficacy while minimizing toxicity, especially in vulnerable populations like the elderly[1, 3,10] The Karnofsky Performance Status (KPS) is also a vital role in assessing a patient's eligibility for intensive treatment. KPS > 70 is usually considered as a cut off to decide eligibility for treatment. However, performance status is not solely based on general health, as neurological impairments caused by the tumor can also contribute to a poor KPS score. [1] Our patient was a frail elderly man with a KPS score of 40. Therefore, the recommended treatment is hypofractionated radiation therapy combined with concurrent temozolomide chemotherapy. A study found that elderly patients receiving hypofractionated doses (such as 40 Gy in 15 fractions) had median survival rates similar to those treated with standard regimens, without significant increases in toxicity[3]. Since older patients often have comorbidities that complicate their treatment, HFRT reduces the frequency of hospital visits and the overall length of therapy, which is particularly beneficial for frail individuals. Management of glioblastoma patients, especially in frail and elderly need holistic treatment. Thus, during radiation therapy, our patient is managed by a multidisciplinary team, including specialists in gerontology, psychiatry, medical rehabilitation, internal medicine, and neurology.

Before he undergoes radiotherapy, we assess his cognitive function. The cognitive assessment results indicate that he got memory impairment (specifically delayed verbal recall), acalculia, and slowed cognitive processing. The memory deficits are associated with peritumoral edema in the right hippocampus, the acalculia is linked to edema in the left parietal region, and the slowed thinking is related to diffuse lesions or widespread peritumoral edema. These findings are taken into consideration when determining the appropriate therapy and are also used

to educate the patient and family regarding potential risks and side effects of the upcoming treatment. As brain cancer rates rise with an aging population, it's crucial for patients and their family to understand potential side effects so they can make well-informed treatment choices. Additionally, identifying delayed or less obvious side effects is equally important. Radiation-induced brain injury (RIBI) is a recognized side effect of radiotherapy for brain tumors, particularly in older adults, and it involves both functional and structural damage to the brain. RIBI progresses through three distinct phases. The acute phase occurs within days of treatment and usually presents with temporary symptoms such as headache and drowsiness, which are caused by cerebral edema and disruption of the blood-brain barrier. The early delayed phase develops within weeks to six months after treatment and may involve reversible symptoms like memory loss, attention difficulties, and fatigue due to transient demyelination. The late delayed phase emerges six months or more following treatment and is often irreversible and progressive, characterized by cognitive decline resulting from white matter necrosis, ongoing demyelination, gliosis, vascular abnormalities, and injury to the hippocampus.[11] Clinicians should assess cognitive function both before and after treatment to detect any existing impairments and identify the specific causes, whether from other conditions, cancer, or radiation. Discussing potential cognitive effects with older patients considering brain radiation supports better communication between doctor, patient and family to make decisions of treatment. Early recognition of side effects can also improve treatment outcomes.

Our patient also underwent chemotherapy with temozolomide. Temozolomide is associated with a risk of opportunistic infections, including Pneumocystis pneumonia (PcP), candidiasis, CMV, herpes viruses, and hepatitis B, with about one-third of affected patients dying. These infections are mainly due to delayed myelosuppression, peaking 5–6 weeks after treatment begins, especially when CD4+ counts fall below 200 cells/μL or total lymphocytes drop below 500 cells/μL. Because lymphocytopenia can last up to 12 weeks after stopping treatment, pulmonary health and

lymphocyte levels must be carefully monitored during prolonged temozolomide use, especially when combined with corticosteroids and radiation, which further increase the risk of infections like PcP.[5] Thus we give our patient PcP prophylaxis with trimethoprim/sulfamethoxazole 480mg p.o. q.d.

CONCLUSION

High-grade glioma (HGG) is a primary brain tumor that grows aggressively and infiltrative. The incidence and mortality rates of HGG increase with age. Individuals aged 65 years or older have a 3.4 times higher incidence and a sevenfold higher mortality rate compared to those under 65 years. The Karnofsky Performance Status (KPS) is the most important prognostic factor in patients over 70 years of age, both before surgery and after treatment with corticosteroids.

To optimize treatment, both in terms of addressing the underlying cause (tumor control) and managing symptoms, a multidisciplinary neuro-oncology team is essential. This team should prioritize patient-centered care by considering several key factors: the feasibility of tumor resection, the patient's functional and cognitive status, existing comorbidities, and the availability of social support. In every decision-making process, it is important to actively involve the patient's family.

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