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How I treat glioblastoma in older patients

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ABSTRACT

Glioblastoma, a WHO grade IV astrocytoma, is the most common primary malignant brain tumor in adults. It is characterized by molecular heterogeneity and aggressive behavior. Glioblastoma is almost always incurable and most older patients survive less than 6 months. Supportive care with steroids and anti-epileptic drugs is critical to improving and maintain quality of life. Young age, good performance status and methylation of the methyl guanyl methyl transferase promoter are important positive prognostic factors. Several recent clinical trials suggest that there is a subset of the elderly with prolonged survival that is comparable to younger patients. Treatment of glioblastoma in older patients includes maximal safe resection followed by either radiation, chemotherapy or combined modality therapy. Recent advances suggest that some patients can avoid radiation entirely and be treated with chemotherapy alone. Decisions about therapy are individual and based on a patient's performance status, family support and molecular features. Future work needs to better determine the role for comprehensive geriatric assessments in this patient population to better identify patients who may most benefit from aggressive therapies.

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1. Introduction

Glioblastoma (GBM), the most common malignant primary brain tumor to afflict adults, is an inexorably progressive and incurable tumor[1]. The current standard of care is defined by the EORTC–NCIC trial that randomized glioblastoma patients to radiotherapy (RT) alone versus combined modality therapy that included radiation and the alkylating chemotherapy,

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temozolomide (TMZ)[2]. Median survival with combined modality therapy was 14.6 months compared to 12.1 months for patients who received RT only. However, no patients over the age of 70 were enrolled. A recent randomized trial examined the addition of alternating electric field therapy with the Optune device and demonstrated an improvement in median overall survival to 19.6 months[3]. This was recently approved by the Food and Drug Administration in the United States and may emerge as the new standard of care. The median age in this study was 57 but did include patients up to the age of 83. While the device has no systemic toxicity, older patients will likely need support to manage skin care, wearing the device and carrying a battery pack that can weigh up to 10 lbs. Despite these advances, population based studies consistently demonstrate that older patients with GBM die earlier and median survival is less than 6 months[4,5].There is no clear standard of care in older patients and treatment regimens are often extrapolated from trials in younger patient populations. Some GBM patients are likely undertreated out of fear of toxicity while others are over-treated in an effort to provide the standard of care.

Patients most often present with seizures, stroke-like symptoms or progressive cognitive decline. In older patients, sudden onset neurologic symptoms are most often confused with stroke. MRI with gadolinium of the brain is superior to computed tomography (CT) in ruling out stroke and demonstrating tumor. MRI is optimal for better delineation of tumor, to evaluate non-contrast enhancing areas of disease, to identify smaller distant enhancing tumors and to make decisions about surgery. Neuroimaging classically demonstrates a heterogeneously enhancing tumor with mass effect and predilection for the corpus callosum. In this urgent setting, clinicians are faced with diagnostic and treatment dilemmas concerning the role of surgery, radiation and chemotherapy in a disease that is fatal, rapidly progressive and can have profound impact on patient function and quality of life.

2. Prognostic Factors

GBM is a disease that preferentially affects older patients and incidence rates increase with age, peaking in the eighth and ninth decades of life[1]. The most important favorable clinical prognostic factors are young age, good performance status and extent of resection[6]. Methylation of the methyl-guanine-methyl-transferase (MGMT) promoter predicts response to alkylating chemotherapy and is critical in identifying those patients most likely to benefit from TMZ[7]. The IDH1 mutation is a diagnostic biomarker for secondary GBM, a tumor that arises from a lower grade glioma, and is associated with improved survival[8]. In older patients, GBM harbors more angiogenic features, has distinct molecular genetics and rarely harbors IDH1 mutations[9–11]. Poor survival in older GBM patients is related to underlying tumor biology, older age and may also be impacted by patient and physician choices about optimal treatments.

A key challenge in managing older patients with GBM is to discriminate those patients that can tolerate aggressive therapies from those that may derive sufficient benefit from single modalities. A comprehensive geriatric assessment (CGA) may help guide patients and physicians to the best treatment options, but little data exists on this in the brain tumor population. Interpretation of a CGA prior to treatment is complicated by the direct impact of brain tumor on language, cognition, balance and motor and sensory functions. Clinical trials for older patients with brain tumors have not incorporated the CGA as standard practice and creating a brain-tumor specific CGA may be beneficial to incorporate in future studies.

3. Surgical Treatment

Although gross total resection is associated with improvement in survival, surgery is never curable and surrounding brain continues to harbor malignant cells[12]. In non-randomized studies, patients who undergo biopsy alone live only a median of 3 to 4 months compared to 7 to 8 months if they undergo a subtotal or gross total resection[13–15]. However, in these retrospective analyses, GTR is likely performed on patients with higher performance status, less frailty and less comorbidities. In patients with significant aphasia, cognitive dysfunction or hemiparesis that is attributable to the tumor, a decision needs to be made about whether tumor removal will improve their neurologic function. This depends on whether symptoms are directly related to the tumor or related to peri-tumoral edema. A multi-disciplinary discussion involving neuroradiology and neurosurgery is often useful and can better define the risks and benefits of resection. Specialized MRI with functional imaging or white matter tractography can also be helpful in surgical planning. In patients with deep, inaccessible tumors, tumors in eloquent areas or significant medical comorbidities, a stereotactic biopsy should be done at minimum to definitively determine diagnosis. Glioblastomas should not be treated empirically and averting a biopsy is only appropriate in patients who definitively choose a palliative approach to care from the outset. I advocate for maximal safe resection in patients with good pre-morbid performance status with the intent to palliate edema, prevent neurologic symptoms and improve survival.

4. Adjuvant Therapy

There are essentially four post-surgical options for GBM in older patients: supportive care alone, RT alone, TMZ alone or combined modality therapy with chemoradiation. Table 1 details survival in randomized studies of newly diagnosed GBM in older patients. A French multicenter study randomized patients over the age of 70 to RT (50 Gy in 1.8 Gy fractions over 6 weeks) or best supportive care and demonstrated a survival benefit from radiation: 29 weeks versus 17 weeks[16]. Measures of quality of life and cognitive function were not worse in the RT group, but in both groups, these measures worsened over time, suggesting that many older patients may be at their best prior to therapy. The median increase in survival of 12 weeks needs to be placed in the context of the burden of 6 weeks of daily radiotherapy. Several studies have aimed to lessen the burden and duration of RT. Conventionally, RT is given over 6 to 7 weeks at a dose of 60 Gy and can result in fatigue that can last for weeks to months after