Management of glioblastoma: a perspective from Nigeria

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Introduction

Glioblastoma (GBM), a grade IV astrocytic tumor, is the most common malignant primary brain tumor and is also described as one of the most aggressive tumor with remarkable a propensity for proliferation. There have been considerable efforts, at understanding the pathophysiology of the tumor, and identifying treatment targets. However, most of these efforts have not yielded the hoped for results, with the 2005 adapted Stupp protocol, still the standard of care for newly diagnosed GBM (1). The prognosis of the disease continues to be poor despite our growing understanding of predictive and prognostic markers.

Epidemiology

GBM is the most common adult glial tumor worldwide. There is a significant variation in the epidemiology of GBM in different regions of the world, with a clear predominance amongst Caucasians compared with the African-Americans (2). Reliable data on the occurrence of GBM in Sub-Saharan Africa and indeed Nigeria is scarce. This may be attributed to a paucity of tumor registries, pre-operative deaths from untreated, symptomatic, large tumors due to cultural and religious beliefs and limited neuropathological diagnosis resulting from a dearth of neuropathologists or general pathologists familiar with the diagnosis of the disease.

Published data, from recent series of small cohort of patients, suggest that meningioma is the most common intracranial tumor among Nigerians (3-5). GBM had been previously reported as uncommon by the forebears of Nigerian neurosurgery (6), and even more so in a report years after this submission (7). There are however more recent reports, that suggest a gradual increase in diagnosis of GBM among Nigerians and GBM reported to be the most common type of glioma as it is in other parts of the world (8,9). The Nigerian patient, presumably presents at a younger age, compared to Caucasians, with advanced disease (9). The reported low incidence of the disease in Nigeria may also be impacted by the absent or non-documentation of some of the established risk factors for GBM such as exposure to ionizing radiations, and low report of familial syndromes such as Lynch and Li-Fraumeni syndromes.

Clinical presentation and diagnosis

The patients in Nigeria usually present late, with significant tumor burden that directly impacts on prognosis (10). Symptomatology are not different from those seen in other populations, with most of the patients presenting with headaches, seizures and focal neurologic deficits. The imaging diagnosis of GBM has improved over the years, with the availability of increasing number of privately driven, high-field MRI machines within the country. Studies are still mainly anatomic, with limited physiologic and functional studies.

Management and outcome

The imaging diagnosis of a possible GBM warranting a surgical consult, should ordinarily lead to the discussion of the case at a multidisciplinary tumor board, to forge a treatment pathway for the patient. This also facilitates the tracking of the patient treatment. Most centers where

GBM is managed in Nigeria do not however have real time tumor boards, often due to lack of appropriate expertise. This makes a case for virtual tumor board which is worth utilizing, especially in the context of having expert views from high volume centers. This concept may be challenged by dearth of infrastructure, but surely, it can be overcome by the currently available technological advances. There is however a significant amount of discussion of patients' care, using real time instant messaging media and e-mails. The ethical issue of confidentiality of patient's health information will continue to evolve but with de-anonymized data, the risk of exposure for patient becomes low.

The standard of care of patients with GBM worldwide, includes surgical resection, followed by the Stupp protocol (11), which has resulted in documented increase in the overall survival (12). There is also a strong suggestion that survival is associated with the race of the patients; being highest in Asians and pacific islanders and lowest in non-Hispanic whites in the United States (13,14). It has also been observed that participation in clinical trials, which is non-existent in our environment, also improves survival in the patients (1). The outcome of patients with GBM in Nigeria however appears to be poorer than seen in other climes and this is due to multiple factors influencing the care of our patients (8).

The extent of resection of GBM has been validated to influence both the overall survival and progression free survival (15,16). There has been advocacy for supra-total resection and lobectomy for temporal GBM (17,18) to further improve prognosis. However varying extents of resections; gross total resection, subtotal resection and surgical biopsy, were reported in the Enugu series in Nigeria, with a debatable conclusion that the choice of surgery did not affect outcome of care (7). We recognize that achieving gross total resection without significant morbidity and compromise of the quality of life of the patient, is limited by the large size of the tumors and the advanced stage of the disease due to delayed presentation from varied reasons (8). Most Nigerian neurosurgical units do not have established protocols for prioritizing the surgical care of patients with GBM, a situation that is complicated by the out-of-pocket payment for treatment and low coverage of the national health insurance scheme, which also has a limited coverage for cancer treatment. While the fatalistic ideas of just committing the patients with GBM to palliative or end of life care has significantly waned among Nigerian neurosurgeons, the capacity of the surgeons to achieve safe maximal resections is sub-optimal due to the limited or non-availability of the surgical armamentarium that have been developed over the years to improve safety and reduce morbidity. Such innovations include awake craniotomy and brain mapping, fluorescence guided resections, and intra-operative MRI/Ultrasound scan (19-24). The latter, which has been previously described as the 'poor man's neuronavigation', has undergone refinement in its application in neuro-oncology, particularly in GBM surgery. However, it still hasn't found a predominant position in the operating rooms within the country despite its versatility and lower cost, mainly due to lack of familiarity with its use and possibly limited availability of the appropriate probes. Thus, the extent of the surgery not only depends on the presentation of the patient but also on the perspectives of the surgeon.

The Stupp protocol has remained the standard of care for the post-operative care of newly diagnosed GBM (1,25), though with different suggestions of modifications such as the 'super-early' initiation of temozolomide (26). The challenge of the post-operative care of these patients in Nigeria is not predicated on just the high cost of temozolomide, especially when considered in the background of a predominant out-of-pocket healthcare payment, by a majorly poor population with a low minimum wage (27,28), but also on its availability. Thus, only a small percentage of patients can afford or maintain the required chemotherapy cycles. Other drugs such as bevacizumab have not demonstrated the hoped results in newly diagnosed GBM. Tumor treating fields (TTFields), which have been approved and gained acceptance, as an addition to maintenance temozolomide, for the treatment of newly diagnosed GBM, with resultant improvement in overall survival and progression free survival (29), is not available within the Nigerian healthcare system.

Most of the definitive pathologic diagnosis of GBM in Nigeria are still based on histopathology results utilizing hematoxylin and eosin staining (7). The average Nigerian patient, does not therefore, benefit from the predictive and prognostic marker evaluations of tissue specimens, a situation that is almost a sin-qua-non with the 2016 WHO modification of the brain tumor classification (30,31). Efforts are however being directed at accessing non-generic kits for these markers to reduce the cost and thus make them more available as part of the patients' pathological evaluation. The post-operative care is further complicated by the limited availability of, and skewed distribution of radiotherapy machines. These are essentially cobalt machines but a few conformal radiotherapy machines and

linear accelerator (LiNAC) have become available more recently with different downtimes between machines (32,33). The challenge created by delayed access to post-op chemotherapy and radiotherapy is early recurrence or progression of the disease, thus, impacting on mortality and morbidity.

Way forward

With a paucity of specialists in neuro-oncology, which is a reflection of the overall shortage in the number of trained neurosurgeons, neuroradiologists, nurses and palliative care specialists in Nigeria (34), making a case for sub-specialty training in neuro-oncology should not be viewed as a luxury, but a fundamental tool, that will help refine, strengthen and direct the care of the GBM patients. Continuing advocacy and engagement with the government and stakeholders on the need for improving access to radiotherapy and chemotherapy will be important. Utilizing technology for virtual tumor boards and low cost intra-operative ultrasound will further improve the care of these patients.

Conclusions

The obvious disparity in the treatment of the Nigerian patients with GBM and those in high income economies, with resultant poorer outcomes, can be reduced. This can be achieved with capacity building in neuro-oncology, increasing advocacy for early detection and presentation, leveraging on technological advancement, as well as increasing stakeholder and government's involvement in the provision of facilities for the care of these patients. These will be important keys to improving their survival.

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