Primary Central Nervous System Tumors in the Aging Population

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Abstract The incidence of primary brain tumors peaks in the aging population, and advanced age is often a prognostic factor associated with shorter survival. In the United States, it is estimated that 69,720 individuals will be diagnosed with primary CNS tumors in 2013, of which 24,560 are expected to be malignant and 45,160 non-malignant. Approximately 50 % of primary CNS tumors are expected to occur in individuals who are 65 years or older. Management of elderly patients with primary brain tumors is challenging because there is no accepted standard of care treatment and this population may have multiple comorbidities, decreased tolerance to treatment, and increased risk for radiation-induced neurotoxicity. This review gives an overview of the treatment options for older patients with glioblastoma and meningioma, the most common primary brain tumors in this population. Treatment of elderly patients with primary brain tumors needs to be individualized, and old age alone should not preclude the use of life-prolonging treatments.

Keywords Elderly · Glioma · Glioblastoma · Astrocytoma · Meningioma · Primary brain tumor · Brain tumor resection · Chemotherapy · Radiotherapy

Introduction

In the United States, it is estimated that 69,720 individuals will be diagnosed with primary CNS tumors in 2013, of which 24,560 are expected to be malignant and 45,160 non-malignant [1]. Approximately 50 % of primary CNS tumors are expected to occur in individuals who are 65 years or older. The incidence rate of both benign and malignant primary CNS tumors is 20.59 per 100,000 person-years in the general

population. The incidence for all primary CNS tumors tends to increase with age and is highest among those 85 years and older (75.27 per 100,000 person-years) [1]. As the population ages, the incidence and absolute number of primary CNS tumors is expected to increase.

The primary CNS tumors histologies especially common in the aging population are meningiomas, malignant gliomas, and primary CNS lymphomas. Despite the high incidence of such tumors in this patient population, there is no clearly accepted standard of care because this aging group is relatively understudied. Moreover, comorbidities, polypharmacy and increased surgical risk add challenges to the management of older patients with primary CNS tumors. In addition, advanced age is the most important prognostic factor associated with poor survival and consequently many clinicians may have a nihilistic approach to such patients.

Glioblastoma

Glioblastoma is the most common and aggressive malignant primary brain tumor. The incidence of glioblastoma increases with advancing age; the incidence is 13.21 per 100,000 person-years in those 65 to 74 and 14.64 between those 75 to 84 years of age, compared to 3.19 cases per 100,000 person-years for the overall population [1].

Prognosis

The survival of older patients with glioblastomas is significantly shorter than their younger counterparts. We showed in a population-based study that the median survival was only 4 months among glioblastoma patients 65 years or older at diagnosis [2], compared with 12 to 14 months in younger patients [3]. This difference in survival is likely multifactorial and includes different underlying tumor biology, patterns of care, treatment tolerability and efficacy.

Glioblastomas are highly heterogeneous tumors at the molecular level. We recently performed a computational

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analysis of the Cancer Genome Atlas (TCGA), a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing sponsored by the United States National Cancer Institute and the National Human Genome Research Institute [4]. We found, for example, that chromosome 10 deletion and chromosome 7 amplification was found more commonly in the old group whereas there was a relatively high frequency of chromosome 1q amplification in the young group of glioblastoma patients [5]. Network analysis of a number of the genes deregulated in older patients with GBMs at either the transcriptional level or at the transcription factor motif enrichment level showed that vascular endothelial growth factor (VEGF), an important pro-angiogenic factor, was more highly expressed in older GBM patients [5]. In addition, some tumor molecular markers associated with longer survival such as the isocitrate dehydrogenase (IDH) mutations and the CpG island methylator phenotype (G-CIMP) are uncommon in the elderly glioblastoma population [6, 7].

Clinical characteristics also are important prognostic factors but the most commonly used prognostic scheme for gliomas, derived from trials run by the Radiation Therapy Oncology Group, excluded patients older than 70 years of age [8]. We reported on a new prognostic scheme derived from 437 patients ≥ 70 years of age with newly diagnosed glioblastoma, pooled from two tertiary North American academic institutions [9•]. Recursive partitioning analysis, which divides patients into successively more homogeneous groups based on survival outcomes, identified 4 prognostic subgroups with markedly different median survivals: subgroup I contained patients 70 to 75.5 years of age who underwent surgical resection (median survival of 9.3 months); subgroup II contained patients ≥ 75.5 years of age who underwent surgical resection (6.4 median survival of months); subgroup III contained patients with Karnofsky performance status of 70 to 100, which denotes independence for daily activities, who underwent biopsy only (median survival of 4.6 months); and subgroup IV contained patients with Karnofsky performance status < 70 (not independent for simple daily activities) who underwent biopsy only (median survival of 2.3 months). This prognostic model was validated in an independent French cohort also resulted in significantly different ($P < .0001$) median survivals for subgroups I (8.5 months), II (7.7 months), III (4.3 months), and IV (3.1 months) [9•].

Treatment

The optimal management of patients over 70 years of age with glioblastoma has not yet been determined and there is no accepted standard of care. The pivotal phase 3 clinical trial demonstrating that chemoradiation with temozolomide

followed by adjuvant temozolomide improved survival compared with radiotherapy alone excluded patients older than 70 years [3].

Maximal safe resection is the accepted initial step of glioblastoma therapy, as it can provide both relief of neurological symptoms through tumor debulking and histological diagnosis. No large prospective randomized study comparing biopsy versus resection has been performed and such trial is unlikely to be ever done, as maximal safe resection has become the accepted standard of care. There has been only one small prospective study of 23 patients aged 65 and older with malignant gliomas, which suggested that resection improved survival compared with biopsy [10]. The tumor resection recommendation, however, is based on retrospective studies showing longer survival, improvement of neurologic function, and quality of life.

A retrospective study of 949 patients who underwent resection for malignant gliomas showed a longer survival of patients who underwent gross total and near-total resection compared with those who underwent partial resection, independent of age, degree of disability, or subsequent treatment modalities [11]. Another retrospective review of 389 patients older than 60 years with glioblastoma diagnosed between 1980 and 1994 showed that surgical resection improved survival compared with biopsy only [12]. We also retrospectively studied 394 glioblastoma patients aged 65 or older and demonstrated that resection had a survival advantage over biopsy [9•].

Post-surgical radiotherapy has been standard practice for glioblastomas based on randomized studies conducted by the Brain Tumor Study Group in the 1970s that showed a survival benefit from radiotherapy (median survival of 36 weeks) compared with supportive care alone (median survival of 14 weeks) [13]. The role of radiotherapy in older patients, however, was still unclear and there was concern for rapid cognitive in older patients undergoing brain irradiation. We reported a US population-based study of 4,137 glioblastoma patients aged 65 and older diagnosed from 1994 to 2002 and found that 78 % of those aged 65 to 69 and only 46 % of those aged 80 and older received radiotherapy [2]. Similarly, a Canadian population-based study showed that only 43 % of glioblastoma patients aged 70 to 79, and only 19.6 % of those aged 80 years or older, received radiotherapy [14].

A prospective randomized clinical trial demonstrated that radiation therapy for glioblastoma patients older than 70 years with good performance status had a modest survival benefit over supportive care alone (median survival of 29.1 weeks versus 16.9 weeks) after tumor resection or biopsy [15]. Even more importantly, this study showed that radiotherapy did not accelerate deterioration in functional, neuropsychological or quality of life assessments; both groups had similar worsening on these parameters, which was more associated with tumor growth [15].

The best regimen of radiotherapy for older patients with glioblastoma is still unknown. For patients who are 70 years or younger, the standard regimen is a 6-week treatment of 60 Gy divided in 30 fractions. In a prospective randomized study, a total dose of 50 Gy to minimize the risk of neurotoxicity in the 70 years or older age group [15] and other abbreviated or shorter courses of radiotherapy have also been studied. Another prospective randomized study compared standard 60 Gy over 6 weeks of radiotherapy with a short-course radiotherapy (40 Gy in 15 fractions over 3 weeks) in 100 patients aged 60 years or older with glioblastoma and found no difference in median survival (5.1 versus 5.6 months) [16]. Importantly, more patients completed the short radiotherapy course (90 % versus 74 %), and short radiotherapy regimen seemed better tolerated as only 23 % of patients required corticosteroid increases, compared with 49 % in the 6-week radiotherapy group [16]. Another more recent randomized phase III trial compared three treatment strategies in 291 glioblastoma patients older than 60 years of age after resection or biopsy: (1) temozolomide (200 mg/m² on days 1–5 of every 28 days for up to six cycles); (2) short-course radiotherapy (34 Gy administered in 3.4 Gy fractions over 2 weeks); and (3) standard radiotherapy (60 Gy administered in 2 Gy fractions over 6 weeks) [17•]. Of patients who underwent the short course of radiotherapy, 98 % completed the proposed treatment while only 76 % of the patients assigned to the standard 6-week of radiotherapy completed treatment. In addition, patients in the 6-week radiotherapy group had the shortest survival (median of 6 months) compared to the short course of radiotherapy (median of 7.4 months) and the temozolomide (median of 8.3 months) groups [17•].

The use of higher dose per radiation fraction that is required for the shorter courses of radiotherapy may be more associated with cognitive decline [18] and this issue has not been clearly studied in this patient population. It has become clear, however, that abbreviated courses of radiation may be appropriate in elderly patients with poor prognosis such as those with poor performance status and those who underwent biopsy only. The exact schedule and total radiation dose are still unclear, but our common practice is to offer a full 60 Gy for patients with good performance status, whereas an abbreviated radiotherapy course may be more appropriate for patients with poor Karnofsky performance status or significant comorbidities [19].

Although the combination of radiotherapy and chemotherapy with the oral alkylating agent temozolomide is the accepted standard of care for patients who are 70 years and younger, the role of chemotherapy in older glioblastoma patients is less established. Our population based study showed that only 10 % of 4,137 glioblastoma patients over 65 received chemotherapy [2]. We also reported a retrospective review of 394 patients with glioblastoma ≥ 65 years of age treated at

Memorial Sloan-Kettering Cancer Center between 1997 and 2007 and showed that 46 % of patients did not receive adjuvant chemotherapy in this tertiary cancer center [20]. This may reflect the fact that the landmark trial establishing the current standard of care for glioblastoma with radiation and concomitant temozolomide followed by adjuvant temozolomide, excluded patients older than 70 years [3] and subgroup analysis did not show any benefit of adding temozolomide to radiotherapy in patients older than 60 years [21].

Retrospective or small prospective studies, however, suggest that older patients with glioblastoma may benefit from chemotherapy in addition to radiotherapy. In a small prospective study of 79 patients with glioblastoma ≥ 65 years of age, there was clear survival advantage of radiation followed by chemotherapy compared with radiation alone (overall survival, 14.9 versus 11.2 months) [22]. Another small prospective single-arm study of 32 glioblastoma patients aged ≥ 70 years with good performance status examined the effect of surgery, radiation, and concomitant and adjuvant temozolomide, similarly to the regimen done in younger patients [23]. The median overall survival was 10.6 months, but 28 % percent of the patients suffered from hematologic toxicity [23]. We also recently reported on a retrospective study of 291 older patients with glioblastoma and combination of radiotherapy and temozolomide was an independent factor associated with prolonged survival in multivariate analyses [24].

More recently, two large randomized phase 3 trials examined the role of temozolomide as an alternative to radiation in elderly patients with newly diagnosed glioblastoma after resection or biopsy. The German study NOA-08 randomized 195 patients 65 years or older with malignant gliomas (89 % with glioblastomas) to temozolomide alone and 178 to the radiotherapy alone (60 Gy over 6 weeks) group [25•]. The median overall survival was 8.6 months in the temozolomide group versus 9.6 months in the radiotherapy group, [25•] showing that temozolomide alone was not inferior to radiotherapy alone in this patient population. Acute toxicity was more common in the temozolomide group but usually reversible and no treatment related deaths were seen [25•]. The Nordic trial randomized 291 patients 60 years or older with glioblastoma to three treatment groups (temozolomide $n=93$, short course radiotherapy $n=98$, standard radiotherapy $n=100$) and 51 of whom were randomized across only two groups (temozolomide $n=26$, short course radiotherapy $n=25$). Median overall survival was significantly longer with temozolomide compared to the standard 6-week of radiotherapy (8.3 months versus 6.0 months) but not different from the short course of radiotherapy (7.5 months). For all patients who received temozolomide or short course of radiotherapy ($n=242$) overall survival was similar (8.4 months versus 7.4 months). For age older than 70 years, survival was better with

temozolomide and with short course of radiotherapy than with standard 6-week radiotherapy [17••].

Glioblastomas with a methylated MGMT (O^6 -methylguanine–DNA methyltransferase) promoter have transcriptional silencing of *MGMT*, leading to low levels of tumor MGMT protein, a DNA repair enzyme. Tumors with methylated MGMT promoter and decreased levels of this DNA repair enzyme MGMT are more susceptible to tumor cell death by alkylating agents such as temozolomide. In contrast, glioblastomas with an unmethylated MGMT promoter have more intrinsic resistance to the tumorocidal effects of temozolomide. Both the German NOA-08 study [25••] and the Nordic study [17••] suggested that evaluation of MGMT promoter methylation seems to be a useful biomarker to predict the usefulness of temozolomide and could potentially aid decision-making. For example, in the NOA-08 study MGMT promoter methylation patients had longer overall than those with unmethylated MGMT promoter (11.9 months versus 8.2 months). In addition, event-free survival was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent radiotherapy (8.4 months versus 4.6 months) while for patients with unmethylated MGMT promoter radiotherapy was associated with longer event-free survival compared to temozolomide (4.6 months versus 3.3 months) [25••].

However, there was no arm in either the NOA-08 [25••] or the Nordic trial [17••] that randomized patients to the standard of care of radiation and temozolomide followed by adjuvant temozolomide. In the United States, older glioblastoma patients with good Karnofsky performance status often are treated identically to their younger counterparts, receiving a 6-week course of radiation with temozolomide followed by adjuvant temozolomide. However, the evidence to support this approach is not based on more definite randomized phase 3 clinical trials. To answer this important question, the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the European Organization for the Research and Treatment of Cancer (EORTC) started a randomized phase 3 trial for glioblastoma patients aged 65 years and older comparing chemoradiation with temozolomide versus radiation alone.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), received accelerated approval for recurrent glioblastoma by the US Food and Drug Administration in May 2009. This approval was based on the rate of durable radiographic responses from two uncontrolled phase 2 trials [26, 27]. Interestingly, one of these trials reported that the median progression-free survival for patients aged 53 years or older was longer than in younger patients (30 weeks versus 11-weeks) [26]. This is the first time that a therapeutic option for glioblastoma seems more effective in the aging

population, as older age is highly associated with shorter progression-free survival and worse outcomes [28]. A retrospective analysis of patients with recurrent glioblastoma also showed that patients 55 years and older derived most benefit from bevacizumab, compared with younger patients [29]. In addition, older patients demonstrated a higher expression of VEGF [26–29], and our computational study also showed that VEGF seems more important in older glioblastoma patients [5]. Two large randomized phase 3 trials of upfront chemoradiation with temozolomide with or without bevacizumab for newly diagnosed glioblastoma have completed accrual and preliminary reports suggest that bevacizumab prolong progression-free survival but not overall survival.

Meningioma

Meningiomas are the most frequently reported tumors and account for more than 35 % of primary CNS tumors [1]. More than 90 % of meningiomas are benign or grade I and the remaining are classified as atypical (grade II) and anaplastic or malignant (grade III). Meningiomas are more than twice as common in women as compared to men. Meningioma has an annual incidence of 7.10 cases per 100,000 individuals in the general population but its rates increase dramatically after age 65 (24.74 cases per 100,000 individuals in the 65–74 population, 35.47 cases per 100,000 individuals in the 75–84 population) and continue to be high even among the population aged 85 years and older (45.11 cases per 100,000 individuals) [1].

Most benign meningiomas tend to grow very slowly and have an indolent course. Tumor growth rate is slower in the elderly. One study reviewed 40 patients 70 years of age or older and found that during an average follow-up of 41-months, 65 % of patients showed no tumor growth [30]. Another study of 244 patients showed that patients who were older than 60 years ($n=136$) had less frequent meningioma tumor growth (33 % versus 55 %) than patients who were 60 and younger ($n=137$) [31]. Although surgical resection is the definitive treatment for surgically accessible tumors, asymptomatic meningiomas discovered incidentally, particularly in the elderly, should be followed with serial imaging. The factors influencing surgical decision are age, tumor size, surgically amenable tumor location, comorbidities, neurologic deficits at presentation, and the possibility of neurologic deficits from surgery [19]. Nonsurgical options such as stereotactic radiosurgery for tumors less than 3 cm in diameter and external-beam radiation also may be considered [19]. Patients with partially resected or unresectable atypical and all those with anaplastic meningiomas may require radiation to prevent tumor recurrence or growth. Overall, the results of chemotherapy or other medical treatments in meningiomas have been disappointing but early phase reports

suggest that antiangiogenic drugs such as bevacizumab [32] and sunitinib [33] may be helpful.

Conclusions

The incidence of primary brain tumors peaks in the aging population, and advanced age is often a prognostic factor associated with shorter survival. Management of elderly patients with primary brain tumors is challenging because there is no accepted standard of care treatment and this population may have multiple comorbidities, decreased tolerance to treatment, and increased risk for radiation-induced neurotoxicity. Nevertheless, there are enough data suggesting that treatment with surgical resection, radiotherapy, and possibly temozolomide chemotherapy may benefit selected elderly glioblastoma patients. Methylation of MGMT promoter may be used as a biomarker to select glioblastoma patients who will most likely benefit from alkylating agent temozolomide. Use of bevacizumab may be more beneficial in older patients but this observation needs to be confirmed by large randomized trials. Meningiomas, especially those asymptomatic, often can be followed with serial imaging, as these tumors tend to have a slow growth rate in elderly patients. Treatment of elderly patients with primary brain tumors needs to be individualized, and old age alone should not preclude the use of life-prolonging treatments.

Compliance with Ethics Guidelines

Conflict of Interest Fabio M. Iwamoto declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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