Primary Brain Tumours in the Elderly

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Primary brain tumours are most commonly diagnosed in elderly individuals and the incidence of these uniformly fatal malignancies is on the rise. Recent studies have shown that the most common of these tumours, the glioblastoma multiforme, is genetically different in elderly compared to younger patients. Current research studies exploiting the genetic differences of these tumours as anti-cancer targets hold promise for the immediate future. At present the focus of brain tumour treatment is excellent supportive care. Radiation treatment and chemotherapy are being actively revisited to maximize quality of life. In addition, complications such as venous thromboembolism, seizures and therapy-induced adverse effects have received much attention and are reviewed in this article.

Key words: brain neoplasms, glioblastoma multiforme, palliative care, chemotherapy.

Introduction

Primary brain tumours represent a small portion of the total primary cancers diagnosed each year in Canada, with an annual incidence of 2,400 cases and over 1,500 deaths.[1] A number of sources indicate this incidence is rising, especially in elderly populations.[2,3] The current trend of an aging population suggests the incidence of new primary brain tumours may continue to rise. Malignant gliomas are the most common primary brain tumours and, despite therapy, their prognosis is extremely poor. The elderly benefit less than younger patients from therapy, and are less likely to be offered treatment.[4] In this article, we summarise the key issues in management of primary malignant brain tumours in an elderly population, and the dilemmas for the future. Although we do not discuss metastatic brain tumours or benign tumours such as meningiomas, many of the supportive care principles discussed here can be generalised to these patients as well.

Brain Tumour Classification

It is likely that brain metastases are slightly more common than primary brain tumours. Of the primary brain tumours, the most frequent are the gliomas—derived from the supporting cells of the brain, or "glia". The most abundant glial cell type is the astrocyte, and tumours derived from astrocytes are called astrocytomas.[5] Table 1 presents a more detailed description of brain tumour classification. The most frequent primary brain tumour is the grade IV astrocytoma, also known as the glioblastoma multiforme (GBM).

Primary vs. Secondary Glioblastoma Multiforme

The evidence suggests that GBMs in older patients are more likely to arise de novo (primary GBM), while those of younger individuals tend to arise from the progression of a lower grade glioma (secondary GBM). The molecular genetics of primary versus secondary glioblastoma are quite different, suggesting that this tumour may represent at least two different diseases with identical histopathology (Figure, page 58).[6]

What is "Elderly"?

Difficulties exist in any discussion of issues affecting older patients. At what age does a person become elderly? Is it purely a function of age that can be set at an arbitrary number, such as Old Age Security at age 65? Or should we consider tumour biology in the definition? There is a very distinct survival advantage for patients younger than 45 years with GBM. Few oncologists would consider a 52-year-old truly the same as an 80-year-old, though their survival curves are, on average, nearly identical. This may reflect the different genetic origins and biologies of primary and secondary glioblastomas.

Therapies

Surgery

All studies of surgery versus biopsy have been retrospective to date, and it is unlikely that there will ever be a randomised controlled trial of these issues. Kelly and Hunt showed a modest survival benefit for resection versus biopsy with and without radiation in elderly patients with grade IV astrocytomas.[7] However, there are numerous confounding factors that would favour resection over biopsy for a patient, such as location of tumour and medical comorbidities.

Radiation

In epidemiologic studies of glioblastoma, the most significant negative prognostic factor has been increasing age. In some patients, expected survival is as long as the proposed radiotherapy course.

The official recommendation of Cancer Care Ontario's Neuro-Oncology Disease Site Group is postoperative radiation therapy in the range of 50–60 Gy for all patients.[8] Lower dose / shorter schedule treatments have been studied, and preliminary data suggest similar survival and quality of life but with less treatment time and resource utilisation.[9,10] A prospective, randomised, controlled trial is currently under way to assess this lower dose / shorter schedule treatment in older patients.

Chemotherapy

Malignant gliomas are not particularly susceptible to chemotherapy. The first modestly successful agents were alkylating agents, particularly the nitrosoureas, carmustine (BCNU) and lomustine (CCNU), and procarbazine. The combination regimen PCV (procarbazine, CCNU and vincristine) eventually

became a "standard" therapy that slightly improved survival for glioblastoma patients.[11] Other agents have been tried with only modest success. Hormonal therapies, such has high-dose tamoxifen are second-line agents. Although there are always studies ongoing, they frequently have exclusion criteria for age, making it difficult to generalise results to older patients.

A harsh reality exists regarding chemotherapy's effectiveness in elderly brain tumour patients. One study showed that less than 5% of patients older than 60 years were likely to respond to chemotherapy, compared to nearly 40% of those younger than 40 years, and their survival was significantly less.[12] Older patients also had a higher rate of complications and mortality from myelosuppression.

Chemotherapy can, however, play a role in the treatment of gliomas in elderly patients. It can provide partial or complete response in selected patients, as well as improved survival. An interesting finding in some of these studies is that the functional performance status of the patients who responded to therapy improved versus those who did not respond.[13]

Less toxic regimens have been developed that provide benefit for elderly patients. Temozolomide is a novel alkylating agent with few side effects that has been approved in Canada for use against GBM. Brandes, *et al.* have studied this agent in the elderly as adjuvant treatment, and have found that it has low toxicity and may show more efficacy than PCV or radiation alone.[14,15]

Consideration is now being given to the possibility of treating elderly GBM patients with temozolomide alone, in order to avoid radiation toxicity. Two studies have shown no significant differences in survival between radiation and temozolomide as monotherapies, in patients who responded to treatment.[16,17] There also was good response in performance status and reduction in dexamethasone dose in the temozolomide-treated patients. Further studies are needed to assess the feasibility of this type of thera-

Table 1

Abridged WHO Classification of CNS Neoplasms

Tumours of Neuroepithelial Tissue

Astrocytic Tumours
- astrocytoma
- anaplastic astrocytoma
- glioblastoma
- pilocytic astrocytoma
- pleomorphic xanthoastrocytoma

Oligodendroglial Tumours
- oligodendroglioma
- anaplastic oligodendroglioma

Ependymal Tumours
- ependymoma
- anaplastic ependymoma
- myxopapillary ependymoma

Mixed Gliomas
- oligoastrocytoma
- anaplastic oligoastrocytoma

Choroid Plexus Tumours
- choroid plexus papilloma
- choroid plexus carcinoma

Neuronal and Mixed Neuronal/glial Tumours
- gangliocytoma
- dysembryoplastic neuroepithelial tumour
- ganglioglioma
- anaplastic ganglioglioma
- central neurocytoma

Pineal Parenchymal Tumours
- pineocytoma
- pineoblastoma

Embryonal Tumours
- medulloblastoma
- primitive neuroectodermal tumour

Tumours of Cranial and Spinal Nerves

Schwannoma
- cellular
- plexiform
- melanotic

Neurofibroma
- plexiform

Malignant Peripheral Nerve Sheath Tumour

Tumours of the Meninges

Tumours of Meningothelial Cells
- meningioma
- atypical meningioma
- papillary meningioma
- anaplastic meningioma

Mesenchymal, Non-meningothelial Tumours
- hemangioblastoma
- hemangiopericytoma
- malignant melanoma

Lymphomas, Hemopoietic Neoplasms

Malignant Lymphoma

Plasmacytoma

Germ Cell Tumours

Germinoma

Choriocarcinoma

Teratoma

Embryonal Germ Cell Tumour

Yolk Sac Tumour

Mixed Germ Cell Tumour

Tumours of the Sellar Region

Pituitary Adenoma

Pituitary Carcinoma

Craniopharyngioma

Metastases of Any Source

Cysts and Tumour-like Lesions

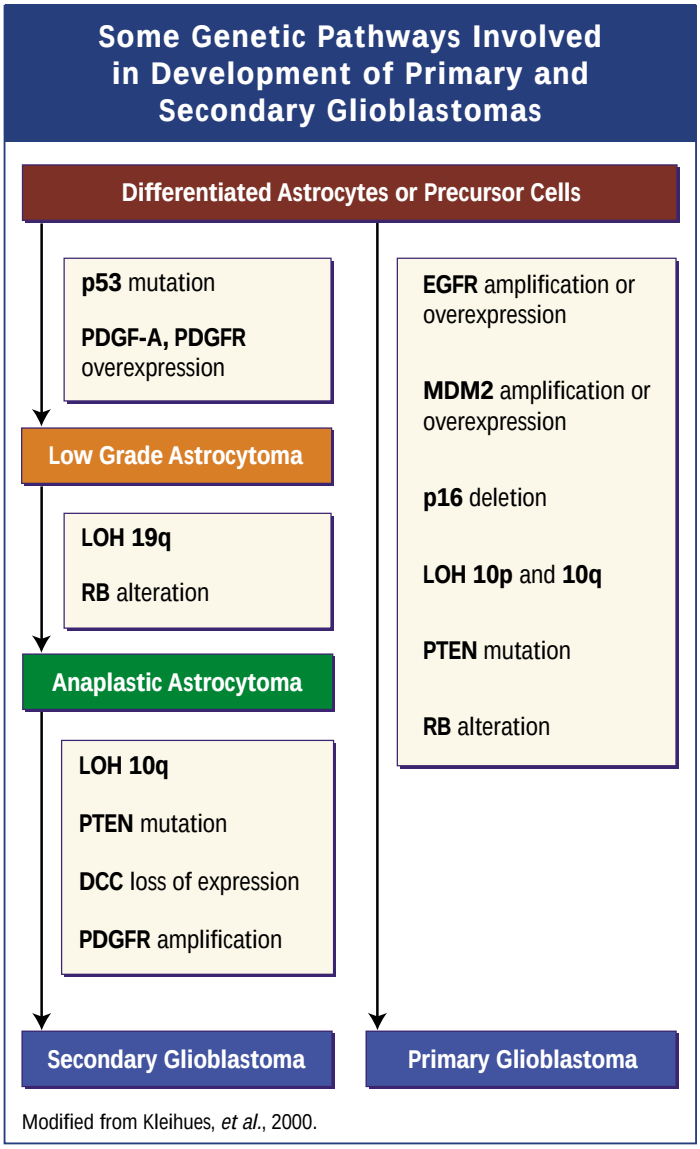
Rathke Cleft Cyst

Epidermoid Cyst

Dermoid Cyst

Colloid Cyst of the Third Ventricle

Modified from World Health Organization Classification of Tumours, 2000.



Modified from Kleihues, *et al.*, 2000.

py. Chemotherapy alone has not been effective in younger patients, reflecting the different biologies of glioblastoma in young and older patients.

Toxicities of Therapy

None of these therapies is without hazards, especially in the older patient. Although advances in neurosurgical techniques and neuroanesthesia have reduced the complication rate, they cannot alter the fact that older brains tolerate injury less well. There is a higher than average morbidity and mortality associated with surgery on elderly brain tumour patients, as well as a high rate of systemic complications.[6,18,19]

Elderly patients have a low tolerance for radiation and its effects on the brain. Increased doses of corticosteroids are required to control edema. In addition, radiation produces significant fatigue in some patients. Patients require frequent rests or naps, and this can be very frightening to the patient and family. Memory pathways also may be disrupted, with short-term memory loss and difficulty assimilating new material. Unlike fatigue, which eventually fades, these symptoms may not disappear and can be very disabling.

Temozolomide has relatively few adverse effects, the most important of which are nausea and vomiting, both easily controlled with standard antiemetics. Antiemetic medications can be very constipating, however, which can worsen pre-existing constipation to uncomfortable levels in the elderly. Severe myelosuppression is uncommon, and rarely cumulative.

Symptomatic/Palliative Treatment

Increased Intracranial Pressure

Symptoms of increased intracranial pressure (ICP) include headaches, especially on awakening, vomiting without significant nausea, blurred vision and reduced level of consciousness. This may be due to tumour bulk with edema or hydrocephalus. The mainstay of therapy for edema is increasing doses of corticosteroids. Dexamethasone is the usual agent, although theoretically other corticosteroids can be used. Oral preparations are preferable, with intravenous being used only if the patient is unable to swallow due to bulbar problems or is comatose. Small increments in dose are rarely helpful if a patient is symptomatic from increased ICP. The dose should be doubled if it is to provide benefit, and then tapered once the patient stabilises. The aim is always to reduce the steroid dose to the minimum that is necessary to avoid neurologic symptoms, and to discontinue when possible. Unfortunately, this cannot always be accomplished.

Long-term use can lead to multiple complications that must be managed. H_2-blockers may be needed for protecting the stomach and duodenum from gastric erosions. Hyperglycemia and overt Type 2 diabetes mellitus may require oral hypoglycemic agents or insulin. Immunosuppression may lead to infections. Prolonged use can produce osteopenia and lead to fractures or avascular necrosis of the hip or shoulder.

Brain tumour patients are particularly prone to seizures either at diagnosis, during or immediately post-surgery, or at any time during further therapy. Elderly GBM patients are less likely to present with seizures than younger patients, and more likely to present with cognitive problems[4] (Table 2). If a patient has never had a seizure, prophylaxis with anti-epileptic drugs (AEDs) will not prevent a first seizure from occurring.[20] The evidence surrounding peri-operative use of AEDs to prevent seizures is controversial. Many neurosurgeons will start an asymptomatic patient on phenytoin or valproic acid at the time of surgery. There are few controlled trials on the topic, but it seems reasonable to attempt to withdraw the medication if the patient has never had any seizures. The cognitive effects of AEDs in the elderly must be considered. The issues surrounding driving and seizures and withdrawal of antiepileptic medications should be discussed in depth with the individual patient, and tailored to accommodate the local regulations.

Palliative Care

Brain tumour patients and their families can benefit from palliative care services. Pain management is not generally a major

need, even though pain is a common fear among brain tumour patients. While headaches can be associated with increasing ICP, the tumour does not cause pain, and the brain parenchyma does not have pain receptors. Headaches due to ICP increases are fairly easily controlled with dexamethasone and standard analgesics.

Immobility is a significant problem for brain tumour patients. It produces bedsores as well as the serious problem of deep venous thrombosis and pulmonary embolism. Low molecular weight heparins have been shown in other solid tumours to reduce the risk of venous thromboembolism,[21,22] and may be anti-angiogenic. Similar studies are currently underway in high-grade gliomas.

Mood disorders are common—as are personality changes—due to the diagnosis and the location of the tumour itself. Frontal lobe tumours may cause significant behavioural changes. Low doses of selective serotonin re-uptake inhibitors can improve motivation and depression. Psychiatric referrals may be of immense benefit in managing patients.

Table 2
Chief Presenting Symptoms by Age Group in Patients with Glioblastoma Multiforme

	18–64 years (%)	65+ years (%)
Headache	30.4	11.5
Seizure	18.6	7.7
Confusion	12.9	14.1
Hemiplegia	6.2	10.3
Aphasia	4.6	11.5
Focal weakness	5.7	8.3
Personality change	2.3	9
Memory loss	3.1	7.1
Gait change	1.5	6.4
Vision change	1.5	0.6
Other	12.9	13.5

Modified from Lowry, *et al.*, 1998.

Primary brain tumours generally do not metastasize outside the central nervous system. Death does not occur as a result of systemic disease, but rather from disease in eloquent areas of the brain, or from increased ICP due to massive CNS burden of disease. Death is generally peaceful.

Conclusion

Primary brain tumours are a significant source of neurologic disability and are increasingly frequent in the elderly population. Life expectancy after diagnosis of high-grade gliomas is extremely poor despite therapy. They are difficult to treat, and treatments have significant morbidity, especially in the elderly. Extensive research is ongoing in this field, although studies have usually ignored older patients. More studies are needed involving patients older than 65 years with high-grade gliomas to determine optimal means of therapy for these patients. Palliative resources are crucial to support the patient as well as the caregiver, who can easily burn out in caring for these extremely ill patients. ◆

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