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Overview

Management of Central Nervous System Tumours in The Elderly

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Abstract

Brain tumours in the elderly show differences from the general population in their spectrum of incidence, their molecular profile and their response to treatment. Furthermore, this population also finds it more difficult to tolerate the treatments applied to younger patients. For these reasons it is justified to investigate older patients separately and to devise treatments applicable specifically to this population. In recent years important information has come from the research literature that allows us to make specific recommendations for the management of elderly patients with brain tumours. Here we review the important publications and document these recommendations.

Key words: Brain tumour; elderly; management

Statement of Search Strategies Used and Sources of Information

We used Ovid Embase and Medline to search the relevant terms for the overview. The resulting references were reviewed and selected for inclusion based on their relevance. Due to the number and breadth of the subjects to be examined in the article, the inclusion of results was not exhaustive, but selective, based on the perceived importance of each article to the topic.

Introduction

The outlook for adult patients with tumours of the central nervous system (CNS) in general deteriorates with increasing age. This is due to a number of factors, which include the different biological behaviour of the tumours, an impaired response of the tumour to treatment and a reduced ability of the patient to tolerate the effects of anti-tumour treatments. That said, outright nihilism is misplaced in the management of elderly patients with brain tumours. Results from recent studies have shown that by defining precisely the clinical circumstance and matching the appropriate treatment, overall outcome in this population can be improved.

The brain is host to a remarkable variety of primary tumours, many with a specific age distribution. Diffuse astrocytomas of all grades can occur in the elderly, but by far the most common is glioblastoma (GBM). On the other hand, tumours generally associated with childhood, such as pilocytic astrocytomas, germ cell and embryonal tumours, are excessively rare in older people [1]. Other commonly occurring tumours include primary cerebral lymphoma and meningiomas [1]. With improved life expectancy, the absolute numbers of 'elderly' people in many populations is increasing, leading to an increase in the number of age-associated brain tumours. It is estimated that the number of cases of GBM diagnosed in the USA will double in the next two decades [2].

The concept of what is meant by 'elderly' is not straightforward and may vary according to disease-specific factors, comorbidity and performance status. For patients with brain tumours, onset of 'elderly' is variably defined

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between the ages of 60 and 70 years [3]. Much of the literature addresses the population of patients aged 65 years and older. However, outcome continues to be age-dependent beyond 65 years and attention must be paid to the age profile and other clinical characteristics in each report before conclusions can be drawn.

Toxicity of Anticancer Treatments in the Elderly

Surgery

Age is one of the major predictors for poor outcome after neurosurgery, although this often reflects an increased burden of comorbid disease rather than the effect of age *per se*. Recent publications suggest that neurosurgery can be offered safely into old age, provided patients are chosen carefully [4].

Radiotherapy

After surgery, radiotherapy is the principle treatment for patients with malignant brain tumours. Acute effects, principally due to treatment-related oedema, occur during and shortly after the radiation exposure and are characterised by symptoms of fatigue, dizziness, nausea and malaise, which can last for some weeks after completion of the course. Although it may be possible to support a younger patient through a prolonged course of radiotherapy, an older person with an incurable disease may find the burden simply too much. As the biology of brain tumours in the elderly often leads to inferior outcomes, approaches that reduce not only the intensity but also the duration of radiotherapy are often recommended.

It has long been assumed that older adults have a lower tolerance to the late effects of cranial irradiation than younger patients. As long ago as 1989, Asai and colleagues [5] showed significantly higher rates of brain atrophy in patients aged over 50 years undergoing whole or partial brain irradiation compared with those under this age. Furthermore, the incidence of atrophy correlated with the volume of brain irradiated. As the aging brain is already susceptible to structural and functional deterioration, it is hardly surprising that the effect of irradiation is more prominent in the elderly. Brandes and colleagues [6] explored this in more depth and concluded that brain irradiation in the elderly should be tailored carefully to the patient's clinical state, particularly their performance status. However, the situation is not as straightforward as sometimes presented. Lawrence *et al.* [7] analysed acute and late neurotoxicity in 2761 patients recruited to 14 Radiation Therapy Oncology Group (RTOG) trials in which they received focal brain irradiation. Although age was an important predictor of toxicity on univariate analysis, this was lost in multivariate analysis, whereas performance status remained important in both assessments.

Chemotherapy

The intact brain is protected from many cytotoxic agents by the blood–brain barrier, although this may be disrupted by the presence of a tumour. There are relatively few publications on the clinical effects of chemotherapy on cognitive function or other adverse clinical CNS effects, when given alone for CNS disease. The largest literature relates to methotrexate-induced leuko-encephalopathy and its associated cognitive deterioration [8], but other agents used in high dose (e.g. nitrosoureas) have also been implicated [9]. Magnetic resonance imaging (MRI) changes in these patients comprise periventricular white matter abnormalities, ventricular dilatation and cortical atrophy. However, their severity does not always correlate with the clinical state. Both the imaging and clinical detriments are worse in older patients [9]. It has been suggested that the effect of chemotherapy is to mimic the aging process through an acceleration of free radical damage, DNA damage and telomere shortening [10]. If this is true, then the more evident effects in older patients are understandable.

As well as treating disease, chemotherapy has adverse effects on other body organ systems. A loss of functional reserve in essential organs leads to a marked reduction in the ability of elderly patients to tolerate chemotherapy regimens during cancer treatment and subsequently to recover completely. However, organ changes occur at different rates in different people and it is important to assess each patient individually to gauge their probable tolerance of any chemotherapy regimen [11,12]. As an example, although a grade 3 and 4 haematological toxicity rate was seen in just 7% of patients younger than 70 years taking adjuvant temozolomide in the defining European Organization for Research and Treatment of Cancer (EORTC) trial [13], the same complication rate was 28% in two subsequent studies of patients aged over 70 years treated with similar regimens [14,15]. Furthermore, medication for comorbid conditions and age-related changes in body composition can also complicate the delivery of chemotherapy regimens.

Treatment of Specific Conditions in the Elderly

Glioblastoma

GBM is the most common primary CNS malignancy in adults, with an increasing incidence with age. The reported European age standardised incidence has increased steadily since the 1970s due mainly to improved detection [16], but has plateaued in the last decade. However, with increasing longevity the number of patients affected continues to rise [2]. It is universally fatal and the survival time for patients treated with surgery and radical radiotherapy alone consistently deteriorates with increasing age [17–20]. For example, Meckling *et al.* [17] reported on 103 non-randomised patients over 70 years of age with high-grade glioma, 67 of whom received postoperative radiotherapy.

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