Clinical Oncology (2009) **21:** 515—524
doi:10.1016/j.clon.2009.05.003

Overview

Combined Radio- and Chemotherapy of Brain Tumours in Adult Patients

C. Nieder*†, M. P. Mehta‡, R. Jalali§

*Radiation Oncology Unit, Nordland Hospital, Bodø, Norway; †Institute of Clinical Medicine, Faculty of Medicine, University of Tromsø, Tromsø, Norway; ‡Department of Human Oncology, University of Wisconsin Hospital Medical School, Madison, WI, USA; §Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai, India

ABSTRACT:
In order to examine the current standards of care regarding combined radio- and chemotherapy for adult patients with brain tumours, a review was carried out of recent studies examining surgery, radiotherapy and chemotherapy in high-grade glioma, medulloblastoma and primary central nervous system lymphoma. The integration of the oral cytotoxic agent temozolomide into current treatment protocols of postoperative combination therapy with radiation and drugs in high-grade glioma is discussed. In glioblastoma, the landmark phase III trial by the European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada has defined the current standard of care. Attempts to optimise the schedule of temozolomide administration and to combine this regimen with additional agents are currently ongoing. Additional trials are examining whether temozolomide—radiotherapy combination regimens should also be the standard of care in patients with anaplastic glioma. The role of postsurgery procarbazine, lomustine, and vincristine (PCV) in addition to radiotherapy in anaplastic glioma with oligodendroglial features is controversial, as two randomised trials failed to show improved survival, despite longer progression-free survival. In medulloblastoma, no comparable landmark trial exists and therefore combined radiochemotherapy must be considered investigational. In primary central nervous system lymphoma, high-dose methotrexate-based chemotherapy is the cornerstone of therapy and the value of consolidation radiotherapy for patients achieving a complete response is controversial, even in younger patients who have a lower risk of neurotoxicity than older patients. The challenges associated with brain tumour treatment remain formidable, but rationally designed clinical trials are gradually leading to improved outcomes.
Nieder, C. *et al*. (2009). *Clinical Oncology* 21, 515—524

Key words: Brain tumours, chemotherapy, glioma, medulloblastoma, radiotherapy, treatment

Statement of Search Strategies Used and Sources of Information

The present review is based on a systematic literature search using Medline (PubMed by the National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA) last accessed 15 February 2009. The key words used were: brain tumour, cerebral tumour, glioma, glioblastoma, medulloblastoma, primary central nervous system lymphoma. The search also included the reference lists of all articles and the appropriate chapters in textbooks on brain tumours and neuro-oncology If several subsequent reports were published from the same institution, the most recent publication was evaluated.

Introduction

Primary brain tumours are a heterogeneous group of diseases arising from different cells of origin and showing characteristic age distributions [1]. Collectively, these tumours represent less than 1% of all cancers in most Western countries. Astrocytoma, one of the most common tumours, can be classified as low grade or high grade. The most malignant, glioblastoma (GBM), or World Health Organization (WHO) grade IV glioma, tends to occur in 50—70-year-old patients, whereas the less malignant forms develop at least a decade earlier. Some data indicate that the median age of GBM patients is higher in developed countries as compared with medium and low resource income countries [2]. The median survival is about 10—15 months for GBM and up to 30—50 months for anaplastic astrocytoma or WHO grade III astrocytoma, despite maximal surgical resection, postoperative radiotherapy and chemotherapy [3]. Comparable figures have been reported from different regions of the world, including countries with limited health care resources [4].

In diffusely infiltrating high-grade glioma, the role of combined radio- and chemotherapy has remained historically controversial. Although these tumours are not curable

0936-6555/09/210515+10 $36.00/0

by any type of monotherapy, several arguments for combined treatment exist. Chemotherapy with different sequentially or simultaneously administered agents can be used to enhance the effect of radiotherapy, aiming either at additive cell kill or true radiosensitisation, or to treat microscopic out-of-field tumour based on the principle of spatial co-operation. The main prerequisites of successful chemotherapy are sensitivity of the tumour cells to the drug and sufficient drug exposure. The key issues of tumour heterogeneity with primary and acquired resistance as well as pharmacokinetics, pharmacodynamics and tumour microenvironment deserve particular attention because of several facts that are specific for brain tumours. First of all, the intact blood–brain barrier (BBB) prevents access to the brain for several compounds. Even in areas of BBB disturbance, as present for example in high-grade glioma, the effects of contemporary drug treatment are not satisfactory. Thus, achieving therapeutic concentrations in distal, seemingly intact areas that are also known to contain infiltrating tumour cells remains an enormous challenge. Various strategies of modified delivery or dose escalation have been explored, including intra-arterial, intrathecal and intratumoral delivery, as well as disruption of the BBB. Convection-enhanced delivery can be used to perfuse regions of the brain with therapeutic agents in a manner that bypasses the BBB. Furthermore, many patients with brain tumours are able to metabolise anticancer drugs more rapidly than other tumour patients because of concomitant enzyme-inducing medications that are necessary to treat or prevent seizures. Phenytoin, carbamazepine and phenobarbital induce hepatic cytochrome P450 enzymes, resulting, for example, in higher maximum tolerated doses of chemotherapeutic and even some molecularly targeted agents. In summary, brain tumours, especially those with high-grade histological features, present unique therapeutic challenges because of their location, aggressive biological behaviour, and diffuse infiltrative growth. Both the tumour and its treatment often result in profound changes in quality of life. Failure of local treatment is still a common feature. Thus, improvement in long-term survival rates will probably require substantial refinements of combined-modality therapy.

High-grade Glioma

Surgical Resection and Postoperative Radiotherapy

Surgical resection remains the initial treatment of choice. Apart from establishing a tissue diagnosis, resection might lead to a rapid improvement in symptoms, e.g. from mass effect, hydrocephalus, etc., and a reduction in steroid requirement. Despite the inability to cure high-grade glioma by surgery, the macroscopic completeness of a 'T1 resection' (referring to the removal of all magnetic resonance-visible enhancing tumour) is generally accepted as being related to survival, although substantial level 1 evidence for this is lacking [5,6].

Historically, early recurrences after resection prompted investigators to study immediate postoperative radiotherapy [7]. It was found that local fields (tumour $\pm$ oedema with 15–20 mm safety margins) are as appropriate as whole-brain radiotherapy (WBRT) and that 60 Gy was better than lower doses [8,9]. Further dose escalation failed to improve overall survival [3]. Today, postoperative radiotherapy is widely accepted as an important and effective way to increase overall survival and the time to progression. In defining the target volume, magnetic resonance imaging fused to computed tomography images adds important information. Intensity-modulated radiotherapy might allow for lower doses to surrounding critical structures, but its true clinical benefit in this disease has not yet been adequately identified. Intensity-modulated radiotherapy is a prerequisite for selective dose escalation to tumour sub-volumes, which might be identified with new imaging methods such as positron emission tomography with various tracers. The hypothesis to be tested here is that biologically more aggressive sub-volumes can be imaged and treated selectively to higher doses. Delays in radiotherapy should be avoided as they might have negative consequences for survival. In the analysis by Irwin *et al.* [10], initiation of radiotherapy after 8 weeks as compared with 2 weeks reduced median survival by 11 weeks for a typical patient. A recent Radiation Therapy Oncology Group (RTOG) analysis of 2855 patients suggested that a 4–6 week delay ('short delay') may not tremendously affect survival [11]. However, these data were derived from study participants and may not be valid for the general population, which probably includes more patients with adverse prognostic features. For patients in unfavourable prognostic groups, e.g. those defined by recursive partitioning analysis [12] or with a new internet-based tool (www.eortc.be/tools/gbmcalculator), hypofractionated treatment to doses of 30–45 Gy over 2–3 weeks is a reasonable alternative to standard conventional radiotherapy due to increased patient convenience and better cost-effectiveness [13]. Especially in countries with poor access to radiotherapy and burdened health care systems, short-course radiotherapy contributes to better use of available resources. Age alone should not be a barrier to treatment. In patients over 70 years of age, radiotherapy as compared with best supportive care significantly improved survival without reducing quality of life or cognition [14].

Postoperative Chemotherapy in High-grade Glioma

Many cytotoxic drugs, most often nitrosoureas and other alkylating agents, have been added to surgery and radiotherapy since the 1970s. They were usually given after the completion of local treatment. A meta-analysis of 16 randomised clinical trials that included patients with different types of high-grade glioma from a 17-year period suggested a moderate increase in survival of 8.6% at 2 years by adding systemic chemotherapy. The median overall survival increased from 9.4 to 12 months [15]. This finding was corroborated by a second meta-analysis of 3004 patients from 12 randomised controlled trials also suggesting a small, but statistically significant, improvement in overall survival from chemotherapy [16]. In this analysis,