clinical practice guidelines

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High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The incidence of malignant glioma is ~5/100 000. Malignant glioma may develop at all ages, the peak incidence being in the fifth and sixth decades of life.

diagnosis

Malignant glioma comprises glioblastoma [World Health Organization (WHO) grade IV], anaplastic astrocytoma (WHO grade III), mixed anaplastic oligoastrocytoma (WHO grade III) and anaplastic oligodendroglioma (WHO grade III). Diagnosis after biopsy or tumour resection is made according to the revised WHO classification. Prognosis depends on tumour grade and histology. Glioblastoma carries the worst prognosis, while pure oligodendroglioma tends to have the best outcome and higher response rates to both chemotherapy and radiation. Prognosis of mixed anaplastic oligoastrocytoma and anaplastic astrocytoma is intermediate between glioblastoma and pure anaplastic oligodendroglioma. Concordance between local diagnosis and central neuropathology review can be as low as 50%, thus careful review of the histology is recommended.

Primary brain tumours only very rarely disseminate outside the central nervous system, thus no systemic staging is required except for differential diagnosis of brain metastasis.

molecular markers

Genetic loss on chromosomes 1p/19q (LOH 1p/19q), recently recognized as a chromosomal translocation has been advocated as a marker for responsiveness to chemotherapy. However, it describes a distinct tumour entity with a prolonged natural history irrespective of treatment. LOH 1p/19q should be performed to support a diagnosis of oligodendroglioma.

Epigenetic silencing of the methyl-guanine methyl transferase (*MGMT*) gene promoter by methylation suggests a partial inability of the tumour to repair the chemotherapy-induced DNA damage. In retrospective analyses it has been correlated with outcome to alkylating agent chemotherapy [II, B]. MGMT determination by immunohistochemistry has been suggested; however, this method lacks standardization, reproducibility and correlation with clinical outcome [III, C]. Short of established alternative treatments and in the absence of clinical consequences routine determination of the *MGMT* promoter methylation status does not (yet) add to the patient management outside clinical trials [V, D]

staging and risk assessment

Staging includes imaging of the brain, ideally by magnetic resonance (MRI). Extent of resection and determination of residual disease should be assessed within 24–48 h after surgery [III, B]. Lumbar puncture is generally not useful, and staging of other organs is not needed. Lower tumour grade, radical tumour resection, younger age (<50 years), good performance status and an intact neurological function, have been identified as more favourable prognostic factors.

treatment plan

Patients should be evaluated by a specialized multidisciplinary team. Special consideration needs to be given to performance status and neurological function. High doses of corticosteroids (usually dexamethasone 8–16 mg/day) allow rapid reduction of tumour-associated oedema and improve clinical symptoms; corticosteroid dose should then be rapidly tapered according to individual needs. The patient's glucose levels need to be

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monitored. Steroids are not necessary in patients without increased intracranial pressure and absence of neurological deficits. There is no need for prolonged steroid therapy after tumour resection or prophylaxis during radiotherapy.

Antiepileptic therapy is indicated in patients presenting with an initial seizure; however, prophylactic antiepileptic therapy before or after surgery is not needed [III, C]. After tumour resection, the indication for anti-seizure therapy should be revisited. First-generation antiepileptic drugs (phenytoin, carbamazepine, phenobarbital and their derivates) are strong inducers of the hepatic metabolism, and may interfere with medications including many commonly used chemotherapy agents (but not with temozolomide). Third-generation agents such as lamotrigine, levetiracetam or pregabalin are preferred.

newly diagnosed patients

surgery. Surgery is commonly the initial therapeutic approach for tumour debulking and obtaining tissue for diagnosis. Tumour resection is of prognostic value; it may be beneficial to attempt maximal tumour resection provided that neurological function is not compromised by the extent of resection [II, C]. When microsurgical resection is not safely feasible (e.g. due to location of the tumour or impaired clinical condition of the patient), a stereotactic serial biopsy should be performed. The diagnostic yield is >95% in experienced hands, moreover molecular genetic analyses (LOH 1p/19q, *MGMT* promoter methylation) can be performed on freshly frozen specimens. Implantation of chemotherapy-impregnated wafers (carmustine polymers) into the resection cavity before radiotherapy has been shown to marginally improve median survival compared with radiotherapy alone in patients who have radical tumour resection [II, B]. However, subgroup analysis did not show significant benefit for patients with glioblastoma. No data are available when compared with standard temozolomide/radiotherapy (TMZ/RT, see below) and there is no information about potential additive value.
radiotherapy. Fractionated focal radiotherapy (60 Gy, 30–33 fractions of 1.8–2 Gy, or equivalent doses/fractionations) is the standard treatment after resection or biopsy [I, A]. Escalating doses beyond 60 Gy has not been shown to be of value. In elderly patients or patients with poor performance status, shorter hypofractionated regimens (e.g. 40 Gy in 15 fractions) are commonly proposed [II, B]. Radiotherapy (28×1.8 Gy, 50 Gy) in patients >70 years of age was superior to best supportive care alone in a randomized phase III trial [II, B].
chemotherapy. Exclusive chemotherapy (usually TMZ) has been proposed for elderly patients, randomized data will be presented at the American Society of Clinical Oncology Annual Meeting in June 2010. For glioblastoma, concomitant chemoradiotherapy is the standard of care. TMZ (at a low dose of 75 mg/m^2) is administered daily (7 days/week) ~1–1.5 hours before radiotherapy from the first to the last day of radiotherapy (usually 40–49 days). Continuous daily administration of TMZ will induce profound lymphocytopenia with CD4 counts <200/mm^3 and this is associated with an increased risk of opportunistic *Pneumocystis* pneumonia. Similarly, steroids will also lower the lymphocyte counts. Prophylactic administration of pentamidine inhalations or trimethoprim–sulfamethoxazole during concomitant chemoradiotherapy should be considered, but is not required during the adjuvant daily ×5 TMZ administration. The blood counts should be monitored weekly, and chemotherapy should be temporarily suspended in the case of thrombocytes <75.000/mm^3 or a neutrophil count of <1500/mm^3. During the maintenance phase TMZ (150–200 mg/m^2) is administered on a daily ×5 schedule every 28 days; blood counts should be checked on days 21 and 28.

glioblastoma (WHO grade IV)

Concomitant and adjuvant TMZ chemotherapy significantly improved median, 2- and 5-year survival in a large randomized trial, and is the current standard of care for patients with glioblastoma up to age 70 [I, A]. No randomized data are available for elderly patients (>70 years) with a good performance status. TMZ is administered daily during radiotherapy, and for 5 days every 4 weeks for six cycles as maintenance (adjuvant) treatment after the end of radiation.

Selecting patients likely to benefit from therapy on the basis of *MGMT* gene promoter methylation has been suggested [II, B], and prospective validation studies have completed accrual. Adjuvant chemotherapy with procarbazine, lomustine and vincristine (PCV regimen) has failed to improve survival in individual prospective randomized studies, both in grade IV and in grade III tumours [I, A]. Nevertheless, based on a large meta-analysis [I, A] nitrosourea-based chemotherapy marginally improves survival.

anaplastic astrocytoma, oligoastrocytoma and oligodendroglioma (WHO grade III)

Anaplastic astrocytoma and oligoastrocytoma have a more protracted clinical course. Standard therapy consists of adjuvant radiotherapy up to 60 Gy after surgery. The value of concomitant and/or maintenance chemotherapy with TMZ has not yet been tested prospectively [V, D]. Randomized clinical trials did not demonstrate prolonged survival with (neo-)adjuvant PCV chemotherapy [procarbazine, lomustine (CCNU)] in newly diagnosed anaplastic oligoastrocytoma and oligodendroglioma [I, B], although progression-free survival was prolonged. Oligodendroglioma characterized by LOH 1p/19q has a more favourable natural history. Early administration of adjuvant chemotherapy before or after radiation did not impact overall survival, despite the exquisite chemo-responsiveness [II, B]. Time to failure of both chemotherapy and radiation was similar whether patients were initially treated with chemotherapy (and receiving RT at first progression) or being treated with initial RT (and administration of chemotherapy at progression) in a randomized trial [II, B]. No difference in efficacy was apparent between PCV and TMZ chemotherapy [III, B].

recurrent disease

Some benefit of chemotherapy has been shown for patients with an adequate performance status who have not received prior adjuvant cytotoxic therapy. Anaplastic astrocytomas are more likely than glioblastoma to respond to TMZ chemotherapy [III, B]. For patients progressing after prior

chemotherapy, there is no established chemotherapy regimen available and patients are best treated within investigational clinical protocols. Single-agent nitrosourea therapy may achieve tumour control in some patients, while randomized trials have failed to demonstrate measurable antitumour efficacy of epidermal growth factor receptor (EGFR) inhibition by erlotinib or platelet-derived growth factor receptor (PDGFR) inhibition by imatinib in an unselected patient population [II, C]. High imaging response rates and a steroid-sparing effect have been observed with administration of bevacizumab (± irinotecan). However, the effect is frequently short lived and may be largely due to changes in vascular permeability. The effect on life expectancy remains unknown [III, C]. On the basis of the available evidence bevacizumab is not currently approved by the European Medicines Agency for recurrent glioblastoma. The indication for re-operation should be evaluated [IV, C]; insertion of chemotherapy-impregnated polymers following repeat radical surgery leads to marginal prolongation of survival in selected patients [II, B].

response evaluation

MRI is the preferred imaging method. Contrast enhancement and presumed tumour progression on imaging 4–8 weeks after the end of radiotherapy may be due to a reactive process following radiotherapy (pseudoprogression) or may be due to true progression and this should be re-evaluated 4–8 weeks later with a second MRI. Apparent increase in tumour size after the end of radiotherapy should not lead to discontinuation of chemotherapy. Response to chemotherapy is evaluated according to the WHO criteria, but should also include an assessment of neurological function and corticosteroid use (Macdonald criteria). The recent introduction of antiangiogenic and vasculature-modifying agents warrants reassessment of response criteria. In addition to contrast enhancement, tumour extension on T2- and fluid-attenuated inversion recovery (FLAIR)-weighted MRI needs to be evaluated. In cases of doubtful differential diagnosis between tumour recurrence and treatment-induced changes (especially after multimodal therapy), positron-emission tomography (PET) with an amino acid tracer (e.g. methionine, fluoro-ethyltyrosine) may be helpful [III, B].

follow-up

Follow-up consists of a clinical evaluation with particular attention to neurological function, seizures and corticosteroid use. Patients should be tapered off steroid use as early as possible. Venous thrombotic events occur frequently in patients with residual or recurrent tumours. Laboratory tests are not indicated unless the patient is receiving chemotherapy (blood counts), corticosteroids (glucose) or antiepileptic drugs (blood count, liver function tests). MRI every 3–4 months is standard practice outside clinical trials, unless more frequent monitoring is clinically indicated.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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