

## Malignant glioma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

R. Stupp<sup>1</sup> & F. Roila<sup>2</sup>

On behalf of the ESMO Guidelines Working Group\*

<sup>1</sup>Multidisciplinary Oncology Center, University of Lausanne Hospital, Lausanne, Switzerland; <sup>2</sup>Department of Medical Oncology, S. Maria Hospital, Terni, Italy

### incidence

The incidence of malignant glioma is approximately 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 tumor resection is made according to the revised WHO classification. Prognosis depends on tumor grade and histology. Glioblastoma carries the worst prognosis, whereas pure oligodendroglioma tends to have a better outcome and improved response to therapy. Prognosis of mixed anaplastic oligoastrocytoma and anaplastic astrocytoma is intermediate between glioblastoma and pure anaplastic oligodendroglioma.

### molecular markers

Genetic loss on chromosomes 1p/19q [loss of heterozygosity (LOH) 1p/19q], recently recognized as a chromosomal translocation has been suggested as a marker for responsiveness to chemotherapy. However, it describes a distinct tumor entity with a prolonged natural history irrespective of treatment, its chemo-responsiveness may be due to the high correlation with methyl-guanine methyl transferase (MGMT) promoter methylation. LOH 1p/19q should be performed to support a diagnosis of oligodendroglioma.

Epigenetic silencing of the MGMT gene promoter by methylation indicates a partial inability of the tumor to repair the chemotherapy-induced DNA damage. In retrospective analyses it has been strongly correlated with outcome to

alkylating agent chemotherapy [II, B]. Alternatively, 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, the routine determination of the MGMT promoter methylation status does not (yet) add to routine patient management [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 by within 24–48 h after surgery. Lumbar puncture is generally not necessary, and staging of other organs is not needed.

Lower tumor grade, tumor resection, younger age (<50 years), good performance status, and an intact neurological function, have been identified as more favorable 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) will allow the rapid reduction of tumor-associated edema and improve clinical symptoms. Patient glucose level needs to be monitored, there is no need for prolonged steroid therapy after tumor 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 in asymptomatic patients [III, C]. After tumor resection, the indication for anti-seizure therapy should be revisited. First generation antiepileptic drugs (phenytoin, carbamazepin, phenobarbital and their derivatives) are strong inducers of the hepatic metabolism and may interfere with many concomitant medications, including many commonly used chemotherapy agents (but not with temozolomide).

### newly diagnosed patients

Surgery is commonly the initial therapeutic approach for tumor debulking and obtaining tissue for diagnosis. Tumor resection

\*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;  
E-mail: clinicalrecommendations@esmo.org

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is of prognostic value; it may be beneficial to attempt maximal tumor resection provided that neurological function is not compromised by the extent of resection [II, C]. Implantation of chemotherapy-impregnated wafers (carmustine polymer) into the resection cavity before radiotherapy has shown to improve marginally the median survival compared with radiotherapy alone [II, B], however no data are available to compare with standard temozolomide/radiotherapy (TMZ/RT, see below).

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 a low 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]. Exclusive chemotherapy (usually temozolomide) has been proposed for elderly patients, but no randomized data is yet available [IV, B].

*Glioblastoma (WHO grade IV)*. Concomitant and adjuvant temozolomide (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 trial data is available for elderly patients (>70 years) with a good performance status. Temozolomide 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 prospective randomized studies, both in grade IV and in grade III tumors [I, A]. Nevertheless, based on a large meta-analysis [I, A] nitrosourea-based chemotherapy may marginally improve survival in selected patients.

*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 temozolomide 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 have a distinct and much more favorable natural history. Early administration of adjuvant chemotherapy before or after radiation did not impact overall survival, despite the exquisite chemo-responsiveness previously described for these tumors [II, B]. Time to failure of both chemotherapy and radiation was similar whether patients are initially treated with chemotherapy (and receiving RT at first progression) or whether patients are treated with initial RT (and administration of chemotherapy at progression) in a randomized trial [II, B]. No difference of

efficacy was apparent between PCV or temozolomide 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 temozolomide 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 improve tumor control in some patients, while randomized trials have failed to demonstrate measurable anti-tumor 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 response rates and a steroid-sparing effect have been observed with the administration of bevacizumab ( $\pm$  irinotecan), however, the effect is frequently short-lived and may be largely due to changes in vascular permeability without necessarily translating into a prolonged survival [III, C].

Repeat surgery and implantation of chemotherapy-impregnated polymers may prolong survival in selected patients [II, B].

### response evaluation

If response is evaluated, it should be done with MRI. Contrast enhancement and presumed tumor progression on imaging 4–8 weeks after the end of radiotherapy may be an imaging artefact (pseudoprogression) and should be re-evaluated 4 weeks later with a second MRI. In case of doubt in patients with early progression after the end of radiotherapy, chemotherapy should be pursued as planned.

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 rate of patients alive and progression free at 6 months (PFS6mo) has been recognized as a valid endpoint and also includes patients who benefit from therapy by disease stabilization. However, with the frequent use of anti-angiogenic and vasculature modifying agents this endpoint may need to be revisited.

### follow-up

Follow-up consists of a clinical evaluation with particular attention to neurological function, seizures or seizure equivalents and corticosteroid use. Patients should be tapered off steroid use as early as possible. Venous thrombotic events occur frequently in patients with unresected or recurrent tumors.

Laboratory tests are not indicated unless the patient is receiving chemotherapy (blood counts), corticosteroids (glucose) or antiepileptic drugs (blood count, liver function tests).

For imaging, MRI is recommended. Repeat 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 experts and the ESMO faculty.

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