

GLIOMAS

General Overview

- Gliomas are a heterogeneous group of tumors arising from glial cells in the central nervous system (CNS), accounting for about 30% of all brain tumors and approximately 80% of malignant brain tumors.
- There are 3 subtypes: oligodendroglioma, astrocytoma and glioblastomas (GBM).
- Diagnosis: contrast enhanced MRI, in selected patients amino-acid PET (FET-PET) can help
- Factors associated with worse outcome:
 - Age > 40 years
 - Tumors > 5 cm
 - Tumor crossing the midline
 - Neurological deficit before surgery
- Many environmental risk factors (non-ionizing radiation (e.g. mobile phones, pesticides, solvents, etc.) have been examined as potential contributors, with inconclusive results.
- Very small portion are caused by a Mendelian disorder (Ollier disease, Maffucci syndrome,...).
- Symptoms: new-onset epilepsy, neurocognitive impairment, signs and symptoms of increased intracranial pressure.

1. OLIGODENDROGLIOMA

General Overview

- Incidence is around 5-8% of all primary CNS tumors. Male/female ratio is around 1.5.
- Found predominantly in the cerebral hemisphere white matter (80 to 90% supratentorial), most commonly in frontal lobes, but temporal and parietal lobe involvement is not uncommon.
- Molecular diagnostic features:
 - IDH (isocitrate dehydrogenase) 1 or 2 mutation
 - 1p19q codeletion = diagnostic biomarker and requirement for the pathological diagnosis (defines oligodendroglioma)
 - Possible additional characteristics (non-obligatory): *TERT promotor mutation, *CIC mutation, *FUBP1 mutation, *NOTCH 1 overexpression

Grading (WHO 2021-CNS 5th edition) and Prognosis

- Grading:
 - Oligodendroglioma, IDH mutant and 1p19q codeleted CNS WHO grade 2 is histopathologically characterized by a so called fried-egg pattern and chicken-wire vessels, with focal microcalcifications and no or very few mitoses.
 - Oligodendroglioma, IDH mutant and 1p19q codeleted CNS WHO grade 3 has high mitotic activity, microvascular proliferation and frequent necrosis.

- Prognosis:
 - Median OS of 10-12 years and 5-year PFS and OS rates of 51-83%.
 - Median OS in WHO grade 3 is 3.5 years

Treatment

- Surgical resection as maximum as feasible (or biopsy if no resection possible). The extent of resection is a prognostic factor! The prevention of new permanent neurological deficits has higher priority than the extent of resection!
- Further treatment is based on risk factors for progression
 - Preoperative tumor size
 - Residual tumor
 - Preoperative enhancement
 - Age > 50 years
 - Grade
 - Deficits caused by the tumor
- Further treatment may exist of radiation and/or chemotherapy, vorasidenib or observation:
 1. RADIATION
 - Grade 2: 50.4 Gy in 28 fractions over 6 weeks
 - Grade 3: 59.4 Gy in 33 fractions at 5 fractions a week
 - Radiation may have an impact on quality of survival because of effects on cognitive function (memory, attention), interfering with independent living in some patients
 2. ADJUVANT CHEMOTHERAPY (FOR ANY GRADE)
 - PCV started 2-4 weeks after radiation (procarbazine 60mg/m² oral day 8-21, lomustine 110mg/m² oral day 1 and vincristine 1.4 mg/m² IV day 8 and 29 in an 8-week cycle for a total of 6 cycles) (cfr. RTOG 9802 trial and EORTC 26951 trial)
 - Temozolomide (TMZ; 150-200mg/m² once daily days 1-5 every 4 weeks for a max of 12 months) can be a reasonable alternative to PCV when toxicity is a concern. There is an increased risk for hypermutated recurrence (due to mutations in mismatch repair genes), there is no clear proof of poorer overall survival. (cfr. CATNON trial)
 - PCV is chemotherapy of choice
 3. OBSERVATION IN SELECTED PATIENTS
 - Low grade (clinical progression may not occur for many years)
 - Low risk: complete resection + age < 40-50 years, specifically for patients without CDKN2A/B deletion.
 - ⇒ Observation can be an appropriate option: MRI every 3 months (to confirm low grade due to risk of underestimating the grade), thereafter every 6 months. Re-resection and/or combined therapy (radiation + chemotherapy) can be an option at progression.
 - ⇒ Watch and wait only after gross total resection and absence of neurological deficits!
 4. Vorasidenib
 - In patients with grade 2 without high risk features and watch and scan is a feasible option, vorasidenib 40mg once daily (compassionate use program)
- Monitor treatment response:
 - MRI every 3-6 months
- Treatment at recurrence or progression:
 - Choice is influenced by the choice of and response to first line therapy.
 - No standard second line. Options:
 - Re-resection should always be considered
 - Re-irradiation

- Chemotherapy:
 1. If prior PCV: TMZ. If prior response to PCV, rechallenge PCV can be an option
 2. If prior TMZ: PCV. If prior response to TMZ, rechallenge TMZ can be an option
 3. Lomustine monotherapy.
- Bevacizumab can be used for symptom control (no clear evidence for antitumor efficacy, no reimbursement, via samples)

What's new

- Phase III with Vorasidenib 40mg once daily (INDIGO trial, NEJM 2023): 331 patients with grade 2 oligo or astrocytoma, mPFS 27.7m. Treatment after surgery for recurrent or residual disease (before radiation and chemotherapy). Compassionate use program ongoing.

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- van den Bent MJ, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021 Jun;22(6):813-823.

2. ASTROCYTOMA

General Overview

- Astrocytomas develop from astrocytes.
- Incidence is estimated at 1/12.500. Slightly predominant male.
- Molecular diagnostic features:
 - IDH (isocitrate dehydrogenase) 1 or 2 mutation
 - Absence of 1p19q codeletion
- Possible additional characteristics:
 - Nuclear ATRX loss (very frequent!)
 - CDKN2A/B deletion

Grading (WHO 2021-CNS 5th edition) and Prognosis

- Grading:

- Astrocytoma, IDH mutant and 1p19q non-co-deleted CNS WHO grade 2; is consistent with low-grade astrocytoma (formerly diffuse astrocytoma). It shows an infiltrative diffuse growth pattern with variable degree of nuclear atypia and pleomorphism and no or very few mitoses.
- Astrocytoma, IDH mutant and 1p19q non-co-deleted CNS WHO grade 3 (formerly anaplastic astrocytoma). It shows increased cellularity and mitotic activity. Necrosis and microvascular proliferation are absent.
- Astrocytoma, IDH mutant and 1p19q non-co-deleted CNS WHO grade 4 (formerly known as IDH-mutant glioblastoma). Frequent CDKN2A/B deletion. Diffuse glioma of astrocytic morphology with increased cellularity, mitotic activity, microvascular proliferation and/or necrosis.
- Prognosis:
 - Depends on histological grade and location (operable or not).
 - Grade 2: median OS around 8 years
 - Grade 3: median OS around 3-5 years
 - Grade 4: median OS around 15 months

Treatment

- Surgical resection as maximum as feasible (or biopsy if no resection possible). The extent of resection is a prognostic factor! The prevention of new permanent neurological deficits has higher priority than the extent of resection!
- Further treatment may differ per histological grade:
 1. GRADE 2
 - Radiation: 50.4 Gy in 28 fractions over 6 weeks
 - Adjuvant chemotherapy with PCV starting 2-4 weeks after radiation (procarbazine 60mg/m² oral day 8-21, lomustine 110mg/m² oral day 1 and vincristine 1.4 mg/m² IV day 8 and 29 in an 8-week cycle for a total of 6 cycles) (cfr. RTOG 9802 trial)
 - Initial therapy may be deferred until radiographic or symptomatic progression in patients with positive prognostic factors (complete resection, younger age < 40 years) or concerns about short- and long-term toxicity. Discuss vorasidenib 40mg once daily in these population (compassionate use program)
 - Vorasidenib 40mg once daily after surgery/biopsy in patients where watch and scan is feasible (compassionate use program)
 2. GRADE 3
 - Radiation: 59.4 Gy in 33 fractions of 1.8 Gy
 - Adjuvant chemotherapy: temozolomide (TMZ; 150-200mg/m² once daily days 1-5 every 4 weeks for a max of 12 months) (cfr. CATNON trial)
 - No deferral of therapy!
 3. GRADE 4
 - No available randomized evidence!
 - Radiation: 59.4 Gy in 33 fractions of 1.8 Gy with or without concurrent temozolomide (75mg/m² oral every day during radiation), followed by adjuvant temozolomide 150-200mg/m² once daily days 1-5 every 4 weeks for a max of 6 months (12 months can be discussed)
- Monitor treatment response:
 - MRI every 3-6 months
- Treatment at recurrence or progression:
 - Choice is influenced by the choice of and response to first line therapy.
 - No standard second line. Options:
 - Re-resection should always be considered
 - Re-irradiation
 - Chemotherapy:

1. If prior PCV: TMZ. If prior response to PCV, rechallenge PCV can be an option
2. If prior TMZ: PCV. If prior response to TMZ, rechallenge TMZ can be an option
3. Lomustine monotherapy
 - Bevacizumab can be used for symptom control (no clear evidence for antitumor efficacy; no reimbursement, via samples).

What's new

- Phase III with eflornithine plus lomustine for patients with first recurrence of anaplastic astrocytoma after RT and adjuvant temozolomide. No clear OS benefit, however, medically meaningful and statistically significant OS and PFS benefits were observed with eflornithine in the pre-planned analysis of patients with molecularly defined 2021 WHO CNS grade 3 astrocytoma.

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3. GLIOBLASTOMA

General Overview

- Incidence is estimated 2-5/100.000. Slight male predominance (1.3)
- Molecular diagnostic features:
 - IDH (isocitrate dehydrogenase) wild type
 - Possible additional characteristics (non-obligatory): *TERT promotor mutation, *gain of chromosome 7, loss of chromosome 10, *EGFR amplifications
 - MGMT promotor methylation status: patients with methylated GBM may have more benefit from TMZ.

Grading (WHO 2021-CNS 5th edition) and Prognosis

- Grading:
 - CNS WHO grade 4.
 - Giant cell glioblastoma, gliosarcoma and epithelioid glioblastoma are all histological subtypes
- Prognosis:
 - glioblastoma median OS 15 months, 2-year survival 27%
 - MGMT methylated: median OS 23 months, 2-year survival 49%
 - MGMT unmethylated: median OS 13 months, 2-year survival 12%

Treatment

- Surgical resection as maximum as feasible (or biopsy if no resection possible). The extent of resection is a prognostic factor! The prevention of new permanent neurological deficits has higher priority than the extent of resection!
- Further treatment may differ according to age and Karnofsky performance status (KPS):
 - Age ≥ 18 and ≤ 70 ; KPS ≥ 70
 - Radiation (eg. 60 Gy in 2 Gy fractions) with concurrent temozolomide (TMZ; 75mg/m² oral every day during radiation), followed by adjuvant temozolomide 150-200mg/m² once daily days 1-5 every 4 weeks for a max of 6 months
 - Age ≥ 70 or KPS ≤ 70
 - Always discuss balance of risks and benefits!
 - MGMT promotor methylated: temozolomide monotherapy can be considered (100mg/m² once daily day 1-7 of every 2 weeks until progression or 200mg/m² once daily days 1-5 every 4 weeks for 6 months). But if possible combination with radiotherapy 40 Gy in 15 fractions is preferred.
 - MGMT promotor unmethylated: radiation monotherapy: hypofractionated radiation (40Gy in 15 fractions)
- Monitor treatment response:
 - MRI every 3 months
- Treatment at recurrence or progression:
 - No standard second line. Options:
 - Re-resection should always be considered
 - Re-irradiation in selected patients
 - Chemotherapy:
 1. Lomustine
 2. Retreatment with TMZ according to time to progression (>3 months **since** last TMZ). Metronomic dosing (50mg/m² daily until progression/intolerance) can be considered.
 3. Regorafenib (no reimbursement, via samples)
 4. NGS based treatment (BRAF, NTRK, ...)
 5. ALWAYS CONSIDER CLINICAL TRIAL!
 - Bevacizumab can be used for symptom control (no clear evidence for antitumor efficacy, no reimbursement, via samples).

Note

- All patients with IDH-wild type 1p19q non-co-deleted gliomas of any grade (molecular glioblastoma, diffuse hemispheric glioma,...) should be treated in the same way as glioblastoma

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- van den Bent MJ, et al. Primary brain tumours in adults. Lancet. 2023 Oct 28;402(10412):1564-1579.
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