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 or observation:

1. RADIATION
   - Grade 2: 54 Gy in 30 fractions over 6 weeks (cfr. RTOG 9802 trial)
   - Grade 3: 59.4 Gy in 33 fractions at 5 fractions a week (cfr. EORTC 26951 trial)
   - 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 (procarbazin 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 toxicitiy 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 years, specifically for patients without CDKN2A/B deletion.
     - ⇨ Observation can be an appropriate option: MRI every 2-3 months (to confirm low grade due to risk of underestimating the grade), thereafter every 4-6 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!

- 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 to be expected.

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- Mohile NA, et al. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline. Neuro Oncol. 2021 Dec 22;24(3):358–83.
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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: 54 Gy in 30 fractions over 6 weeks
     - Adjuvant chemotherapy with PCV starting 2-4 weeks after radiation (procarbazin 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.
  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 1.88 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
- 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 to be expected.

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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 (however there are insufficient data!).

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).
        - 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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