Guidelines for molecular testing in gliomas

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EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma

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Markers

- Three molecular markers (1p/19q co-deletion, MGMT promoter methylation, IDH1/2 mutation) are valuable prognostic markers
- The role of clinical decision making at present is mostly restricted to
  - MGMT promoter methylation in elderly patients with glioblastoma
  - 1p/19q co-deletion in patients with anaplastic oligodendroglial tumours

Weller et al, Lancet Oncology 2014
NOA-8 trial: RT versus TMZ in elderly GBM patients

- 373 elderly patients randomized between RT and temozolomide (1 one week on/one week off schedule)

- EFS in patients with MGMT promoter methylation: longer in TMZ treated patients
  - 8.4 months [95% CI 5.5-11.7] vs 4.6 mo [4.2-5.0] after RT

- MGMT unmethylated: opposite finding
  - 3.3 months [3.0-3.5] vs 4.6 months [3.7-6.3] after RT

Wick et al, NOA-8 trial
RT versus TMZ
Overall survival 1p/19q deleted
HR: 0.56, 95% CI [0.31, 1.03]
P = 0.059

Overall survival 1p/19q intact
HR: 0.83, 95% CI [0.62, 1.10]
P = 0.19

Conclusion: In 1p/19q co-deleted tumors clinically significant benefit of PCV
Erasmus MC glioma testing: Next Generation Sequencing (Ion Torrent)

Molecular examination conducted in

- grade II and III diffuse glioma patients
- Glioblastoma in patients ≤ 50 jr
  - (secondary = IDH mutated glioblastoma?)
- Recurrent glioblastoma, candidates for targeted treatments
  - EGFR ampl, MDM2 ampl, PTEN mut, C-Met ampl
- Diagnostic riddles with a distinct possibility of a diffuse glioma
Targeted Next Generation Sequencing as routine diagnostics

• Next generation sequencing
  – CNA: 1p,19q, 7, 10q, EGFR (ampl)
  – Murations: IDH1, IDH2, EGFR, PTEN, TP53, ATRX, TERT, NOTCH, CIC, FUBP1

• Definitions:
  – Oligodendroglioma: 1p/19q codeletion (entire arm)
  – Astrocytoma: IDH mutation, no 1p/19q co-deletion
  – Glioblastoma: TERT mutation but no 1p/19q loss, or trisomy 7/EGFR amplification and /LOH 10q
Some results of targeted NGS in diffuse glioma

• Panel validation in 137 mainly FPPE cases from EORTC 26951
  – All locally diagnosed anaplastic oligodendroglialoma
  – In 91% molecular diagnosis obtained

• 50 cases with 1p/19q co-deletion
  – 49 showed IDH mutation & TERT mutation
  – NGS much more sensitive than FISH (only 30 cases)

• 20 astrocytoma (IDHmut but 1p/19q intact)
  – 19 with TP53; ATRX mutation in 13 (65%)
Overall survival in Molecular and Histological classified tumors

Molecular subtypes

- Comparison with multivariate analyses of the prognostic impact of the molecular classification versus central study review diagnosis
- In these analysis only the molecular classification was selected
Prognostic impact of molecular factors

• Statistically significant prognostic factors for OS in multivariate Cox regression analysis:
  – the presence of TERTmut-1p/19q intact (p<0.0001, HR 4.04, 95% CI 2.36, 6.88)
  – TERTmut-1p/19q co-deleted (p=0.04, HR 0.57, 95% CI 0.33, 0.99)

• CTREE analysis:
  – IDH the most significant prognostic factor (p < 0.001)
  – with LOH 10q as a 2nd factor (p = 0.01)
Seizures and multiple lesions on T2 weighted imaging

- 57 year old female
- Seizures, progressive weakness left arm, left sensory signs
- Multiple abnormalities on T2 weighted imaging
- No enhancement, some increase rCBV
- Biopsy: Astrocytoma gr II
- NGS: PTENmut, EGFRampl, IDHwt
- Glioblastoma!
Some general remarks

• Next WHO Classification based on molecular findings?
  – Improved prognostication & classification
  – Grading will remain ‘conventional’
• Combined IDH and 1p/19q diagnostics already covers a lot
  – IDH IHC only 90% sensitivity
  – 1p/19q loss: entire arms!!!
• MGMT: quality assurance program …
The NEXT WHO classification??

- Classification should be based on molecular findings
  - Improved prognostication & classification
- Grading will still be based on conventional histopathology
- Combined IDH and 1p/19q diagnostics already covers a lot
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- MGMT: quality assurance program …
No quality without you…