Lower grade glioma: future developments

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WHO 2016 glioma classification

**Histology**
- Astrocytoma
- Oligoastrocytoma
- Oligodendroglioma
- Glioblastoma

**IDH status**
- IDH mutant
- IDH wild type

**1p/19q and other genetic parameters**
- ATRX loss*
- TP53 mutation*
- 1p/19q co-deletion

**After exclusion of other entities:**
- Astrocytoma, IDH wild type
- Oligodendroglioma, NOS
- Glioblastoma, NOS

* = Characteristic but not required for the diagnosis

Astrocytoma IDHwt no single entity: requires further molecular diagnostics

- 166 IDHwt cases from a series of 718 WHO II/III patients; OS in H3F3A, TERT or EGFR mutated: median OS 1.23 yrs\(^1\)

<table>
<thead>
<tr>
<th>All Tumors (n = 166)</th>
<th>TERTp mut (n = 41)</th>
<th>BRAF-V600E (n = 10)</th>
<th>EGFR amp (n = 20)</th>
<th>H3F3A-K27M (n = 12)</th>
<th>H3F3A-G34R (n = 2)</th>
<th>MYB amp (n = 33)</th>
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- Erasmus MC experience\(^2\)
  - 639 cases, assessed with NGS panel, with assessment CNA 7, 10; and assessment TERT promoter mutations
  - 74 IDHwt: 39 7+/10q- (38 TERTp mt), 14 only TERTp mt
  - Prognosis even worse in TERTp mt only

A modified WHO 2016?

IDH mutated glial precursor

- TP53 mut
- 1p/19q codel

IDH mutated 1p/19q intact
- low grade astrocytoma
- anaplastic astrocytoma
- grade IV astrocytoma?

IDH mutated 1p/19q codeleted
- low grade oligodendroglioma
- anaplastic oligodendroglioma

7+/10q- glial precursor

IDH wt glioblastoma
- Grade 2, 3 7+/10q LOH
- IDH wt glioblastoma

Type
- grade 2
- grade 3
- grade 4

Grade II, III and:
- TERT mutated only?
- IDH wt and no other lesions?
Current state of affairs in lower grade glioma

- In IDHmt glioma, standard of care is resection, followed by radiotherapy and chemotherapy
  - Decision for (type of) further treatment influenced by tumor grade, extent of resection, age
  - Limited sensitivity of 2nd line chemotherapy and of chemotherapy at PD after radiotherapy
- Not all low grade glioma are IDHmt
  - BRAFmt, BRAF-KIAA fusion, FGFR1mt: options?
  - Some are resembling glioblastoma… treat them accordingly!
The challenge: trial design in low grade tumors

- Clinical endpoints mature very slowly (10-15 yrs)
- Responses usually limited in magnitude despite clinically relevant stabilization
- Time until a 25% increase is observed will not reflect ‘true PD’ in a continuously growing lesion…
  - Alternative: mean tumor diameter curves?
- Uncontrolled studies subject to biases and lack of well established endpoints!

- Alternative endpoint: change in growth rate?

➢ Good trial conduct major challenge
Beyond classical chemotherapy: new targeted approaches in IDHmt glioma?

- mTOR inhibitors? Temsirolimus (ongoing studies)
  - Based on upregulation mTOR signalling, loss of PTEN function (methylation)
- IDH antagonists?
  - Pivotal mutation, leading to reduction ketoglutarate and increased 2-hydroxyglutarate, leading to functional alterations
- PARP inhibitors in IDHmt tumors?
  - Based on the induction of dsDNA breaks by 2HG
- Immunotherapy?
Mutated IDH gene produces protein with altered substrate affinity

- Decreased levels of α-ketoglutarate, accumulation of 2-HG
- 2HG assumed to be oncprotein
  - 2HG inhibits a wide range of α-KG dependent dioxygenases
  - Epigenetic dysregulation via inhibition of αKG-dependent histone and DNA demethylases, resulting in CIMP
    - In 90-95% incl MGMT methylation
  - Block of cellular differentiation, pathological self renewal of stem like progenitor cells?
- Upregulation PI3K/mTOR signaling
- Contributes to the immosuppressive landscape of gliomas

Still unclear whether IDH mutation by itself causes cancer or if it requires other oncogenic events to initiate tumorigenesis
The IDH paradox: a driving mutation causes a treatment sensitive glioma

- In vitro studies show that expression of the IDHmt sensitizes cells to ionizing radiation
  - Related to NADHP depletion?
- IDHmt cells more sensitive to chemotherapy
  - Related to MGMT promoter methylation?
  - Disruption of other $\alpha$-ketoglutarate depending enzymes?
- Other DNA repair mechanisms disturbed? Opportunities?
  - 2HG induces DNA double strand breaks? Opportunity for synthetic lethality?
  - Decreased functioning of NAD+ depending PARP-1 associated DNA repair pathways?
Targeting IDHmt cells

- Are the cell alterations induced by the IDH mutation targetable in glioma?
  - Reversing IDHmt metabolic changes: back to normal?
  - Exploiting IDHmt induced metabolic changes: double the trouble?
IDHmt protein inhibitors: an emerging class of agents

- Several novel compounds target IDHmt protein
  - AG120, AG-5198, IDH305, BAY1436032 (pan-mutant IDH1 inhibitor), AG-881 (brain penetrant)
  - Basic mechanism: restoration of intracellular 2HG levels
- Impair growth, increase survival in various (but not all) cell lines and animal models
- Clinical efficacy of enasidenib (IDH2 inhibitor AG-221) demonstrated in refractory AML
  - 19.7% CR, by inducing differentiation, not through cytotoxicity
- Glioma data so far less impressive: mutation on histological/organ context?

AG-120, A First-in-Class Mutant IDH1 Inhibitor in Patients with Recurrent or Progressive IDH1 Mutant Glioma: Updated Results from the Phase 1 Non-Enhancing Glioma Population

- Median treatment duration: **16 mos**
- 63% of patients treated for ≥ 1 year
- Median PFS for ALL non-enhancing patients = 13 mos (not reached for WHO grade II subset)

- **AG-5198 activity in unenhancing tumors?**

Data presented by Dr Mellinghoff, SNO 2017
Mechanisms of temozolomide and nitrosourea’s

- Primarily effect alkylation/methylation at the O⁶ position if guanine,
- Repair by MGMT, requires intact MMR
- However: Base Excision Repair also relevant for repair of single strand DNA breaks
2HG Inhibits ALKBH DNA Repair Enzymes and Sensitizes to Alkylating Agents

- AlkB homolog DNA repair enzymes repair methylated lesions such as 1-methyl adenine and 3-methyl cytosine
  - α-ketoglutarate dependent hydroxylase
  - Involved in the resistance against TMZ
- ALKBH DNA repair enzymes are inhibited by 2HG
- Contributes to sensitivity of IDH mutated tumors to TMZ, CCNU
  - Inhibiting 2HG may result in decreased response to TMZ, lomustine
- AG-881: In oligodendroglioma mouse model no antagonistic effect of AG-881 on TMZ efficacy

Radioprotection of IDH mutant cell lines by the IDH inhibitor AGI-5198?

- Decreased NADPH production by IDHmut cells make cells more sensitive to RT (in vitro)
  - Increases oxidative stress
  - Same effect of 2HG: Inhibition of α-KG?
  - Is inhibited by AGI-5198: restores NADPH, reduced sensitivity to RT

RT with IDHmut inhibitor may decrease efficacy of RT!

- Data not confirmed by in vitro study on non-brain penetrant AG-120
  - Clear reduction of 2HG,
  - In combination with RT no effect on RT efficacy
  - However: no single agent effect of AG-120

Molenaar et al, Cancer Res 2015;75; Nicolay et al, SNO 2018 EXTH-59
PARP inhibitors and IDHmt glioma

- Intrinsinc double strand repair deficiency in IDHmt tumors
  - Related to 2HG, results in ‘BRCA-ness’ of the tumor
  - Inhibition of BER by PARP inhibitors results in synthetic lethality

- IDHmt cells characterized by vulnerability to co-enzyme NAD+ depletion
  - Essential for BER, result of inhibition of nAMPT1 enzyme
  - Essential part of the PARP complex: cells more vulnerable to PARP inhibitors?

Some conclusions and questions: do the models deliver?

- Results vary between studies, incl impact on 2HG production, on intracellular changes of IDHmt inhibitors, on effects of intracellular 2HG administration
- The used in vitro models vary, most use existing cell lines in which an IDHmt is introduced (eg, U87, U251, HELA, HCT116): biological relevance? Context of cell/tissue of origin?
- IDHmt tumor cells difficult to culture, in case of succes: why this one? Indeed representative for ‘normal’ IDHmt glioma?
- To what extent are model findings influenced by cellular/genetic/organ context? Context development specific later mutations?

- Fundamental question: IDHmt pivotal for gliomagenesis, but also still required for clonal expansion at the time of further progression?
  - From driver to passenger mutation?
A role for PI3K/mTOR inhibitors? A trial on everolimus

- Activation of PI3K pathway common in LGG
  - Partly result IDH mutation effects
- Trial on 58 pts (22 codel), inclusion required resection (subtotal or biopsy) for progression
- PF-6: 84%; 27 pts completed one year of therapy without PD
  - 23 of which had grade II tumors;
- However: no control arm, PD required 25% increase variable patient population
  - Different prior treatments, 19% only surgery, 35 subtotal resection, 47 still grade II at start
  - Do we know this patient population well enough to do an uncontrolled trial?
  - Objective response as measure of success required?

Wahl et al, Cancer 2017;4631-9
BRAF mutations: an actionable target

- BRAF mutations: frequent in (anaplastic) PXA (43-66%), ganglioglioma (18-43%), epitheloid glioblastoma and pilocytic astrocytoma (especially non-fossa posterior: 33%)

- Should be routinely investigated in any of these diagnosis

BRAF mutated glioblastoma before and after 4 cycles of combined RAF and MEK inhibition
FGFR1 actionable mutations in adult midline gliomas

- Series of 116 midline gliomas in patients > 15yrs, median 46.5 yrs
- In 18% FGFR1 mutation, N546 and K656
- all H3F3Awt and IDHwt, and associated with ATRX loss
- Previously reported in wide arrange of histologies
- Several highly specific oral FGFR inhibitors in clinical trials (e.g., TAS-120)

- 45 year old patient, histology: pilocytic astrocytoma, NGS: mutations in FGFR1 & ATRX, imbalance 7 + 10, partial 9; IDHwt
- Methylation array: tumor clusters with anaplastic pilocytic astrocytoma

Picca et al, Neurology 2018 http://dx.doi.org/10.1212/WNL.00000000000005658
Mutational load predictive of outcome to anti-PD1 treatment?

- Pembrolizumab in NCSLC: outcome related to high mutational load and *high neo-antigen burden*, even in case of low PD-L1 expression
- Pembrolizumab, nivolumab registered by FDA for use in MSI-High or MisMatch Repair deficient tumors regardless of organ of origin
- Lasting and objective response rates in 30-40% range in organ agnostic trials

Temzolomide induced hypermutation

- Newly diagnosed glioma in general low mutational load
- A subset of TMZ treated IDHmt glioma and IDHwt glioma recur with MMR deficiency and high mutational load
  - 6:10 TMZ treated glioma recurred with high mutational load
  - Efficacy anti-PD1 treatment?
    - To be established in clinical trials

A mutation-specific peptide vaccine targeting IDH1R132H in patients with newly diagnosed malignant astrocytomas (NOA-16) Platten et al, ASCO 2018 abstract #

- Preclinical studies identified IDH1R132H as a clonal neoantigen presented on MHC class II to induce tumor-specific therapeutic T helper cell responses
- Phase I project on 32 patients on safety and immunogenicity of a mutation-specific IDH1R132H peptide vaccine
- 28/30 patients displayed IDH1R132H-specific T cellular or humoral immune responses not detectable before vaccination
- 12/32 (37.5%) patients evidence of pseudo-progression
- Single-cell T cell receptor (TCR) sequencing allowed for the identification of IDH1R132H-specific TCRs
Conclusions

- We are still left behind…
- How to best exploit IDHmt still to be clarified
  - Go with the flow? Against the flow?
- FGFR1 mutations?

- BRAF V600E mt is actionable: should be routinely tested for
  - Novel BRAF inhibitors also targeting BRAF-KIAA are under development

- Anti-PD1 treatment in MSI high glioma to be investigated
  - Should be routinely tested for in recurrent glioma