Ultra-mutated IDH-wild-type glioblastomas in patients younger than 50 years have peculiar histopathology and better prognosis

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Background

Glioblastoma (GBM) (WHO 2016):

- *IDH* mutant

- *IDH*-wt
  - main incidence > 55 years
  - Relatively rare in adults 18-55 years
  - worse prognosis 🙁
  - *EGFR* ampl/mut; *PTEN* deletions; *CDK2NA* deletions 🧪
Background: *IDH-wt GBM*

Survival < 18 months in spite of treatment

No long-term effective therapies

Lack of molecular studies in the subgroup young adults (< 55 years)
Aims

To investigate the mutational spectrum of IDH-wt GBMs in adults < 55 years

and

Possibly, to identify new therapeutic targets in this subgroup of patients with longer (age-related) life expectancy
Patients

Retrospective study on
16 untreated IDH-wt GBMs FFPE in adults <55 years (24-49 yrs)
  o 1 epithelioid
  o 1 giant cell
  o 3 with > 20% dispersed giant cells (25%, 50% and 50%)

Clinical features
  o 1 patient (giant cell GBM) with prior breast cancer
Methods (I)

NGS (Ion Torrent): Oncomine Tumor Mutational Load (TML) Panel of 409 genes
  - Mutations
  - Copy Number Variation (CNV)
  - Tumor Mutational Load (TML) (n mutations/Mb)
  - Mutational signature
Methods (II)

- Polymerase $\xi$ (\textit{POLE}) and $\delta_1$ (\textit{POLD1}) mutations (NGS; Ion Torrent)
- MSI
- MMR proteins immunohistochemistry
- Disease specific survival (DSS) analysis according to molecular features
Results: most common molecular alterations
Results (TML): frequency of hyper- and ultramutation

- 8 GBMs (50%) hypermutated* (> 9 muts/Mb)
- 2 GBMs (12.5%) ultra-mutated* (> 100 muts/Mb)

* Campbell et al. Cell 2017, 171, 10421-1056
Results: ultra-mutated GBMs have MMR mutations, MSI and giant cells

- 1 giant cell GBM
  - 2 somatic $MSH2$ mut (1 truncating; 1 missense)
  - High MSI

- 1 GBM with 25% giant cells
  - Somatic $MSH6$ mut (truncating Glu1322Ter)
  - High MSI

NO OTHER CASES HAD MMR MUTATIONS AND/OR MSI
Results: ultra-mutated GBMs have MMR mutations, MSI and giant cell
Results: 1 ultra-mutated GBM with *POLE* mutation

- 1 GBM with > 25% dispersed giant cells
  - somatic *MSH6* mut
  - High MSI
  - Germline *POLE* Arg742Cys (exon 20) in polymerase domain not previously reported in GBM (uncertain significance in PolyPhen database)
Results: 1 ultra-mutated GBM with \textit{POLE} mutation

\textit{POLE} mutations
- Associated with ultra-mutation
- Most common in proofreading domain
- Mutational signature with C>A transversions peaks
Results: 1 ultra-mutated GBM with **POLE** mutation

Associated with POLE + MMR impairment in COSMIC (https://cancer.sanger.ac.uk/signatures_v2)
Results: Hyper-mutated GBMs have better prognosis

Hypermutation was the only prognostically significant molecular variable

$P = 0.04$
Conclusions

• Ultra-mutated GBMs have MMR mutations, MSI and giant cells enrichment (> 20% giant cells)

• Ultra-mutated GBM can show POLE mutation in the polymerase domain

• Hypermutated GBMs have significant better prognosis than non-hypermutated GBMs
Potential clinical impact

Ultra-mutated *IDH-wt* GBMs might be candidates for immunotherapy and recognized by:

- giant cell enrichment
- Defective MMR/MSI
Thank you for your attention

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