ScienceDirect

Cancer Letters

Available online 27 February 2024, 216711

In Press, Journal Pre-proof What's this?

Original Articles

Clinicopathological and molecular landscape of 5-year IDH-wild-type glioblastoma survivors: A multicentric retrospective study

Evelina Miele [a 1], Elena Anghileri [b 1], Chiara Calatozzolo [c 1], Elisabetta Lazzarini [d], Sara Patrizi [a], Andrea Ciolfi [e], Lucia Pedace [a], Monica Patanè [c], Luana Abballe [a], Rosina Paterra [b], Luisa Maddaloni [b], Sabina Barresi [f], Angela Mastronuzzi [a], Alessandra Petruzzi [b], Irene Tramacere [g], Mariangela Farinotti [h], Lorena Gurrieri [i], Elena Pirola [j], Mauro Scarpelli [k], Giuseppe Lombardi [l]...Bianca Pollo [c]

Show more

Share Cite

https://doi.org/10.1016/j.canlet.2024.216711

Get rights and content

Highlights

- This is a multicenter retrospective study on a large cohort of GBM-LTS patients.
- The mutational profile of pathogenic variants and CNV was similar in LTS and STS.
- LTS show no episignature but a global higher methylation in CpG islands.
- Methylation levels of distinct gene promoters correlated with prognosis.

Abstract

Five-year glioblastoma (GBM) survivors (LTS) are the minority of the isocitrate dehydrogenase (*IDH*)-wild-type GBM patients, and their molecular fingerprint is still largely unexplored. This multicenter retrospective study analyzed a large LTS-GBM cohort from nine Italian institutions and molecularly characterized a subgroup of patients by mutation, DNA methylation (DNAm) and copy number variation (CNV) profiling, comparing it to standard survival GBM. Mutation scan allowed the identification of pathogenic variants in most cases, showing a similar mutational spectrum in both groups, and highlighted *TP53* as the most commonly mutated gene in the LTS group. We confirmed DNAm as a valuable tool for GBM classification with a diagnostic refinement by using brain tumor classifier v12.5. LTS were more heterogeneous with more cases

classified as diffuse pediatric high-grade glioma subtypes and having peculiar CNVs. We observed a global higher methylation in CpG islands and in gene promoters of LTS with methylation levels of distinct gene promoters correlating with prognosis.

Introduction

Glioblastoma (GBM) is the most common primary brain tumor and a clinical challenge, with one of the worst 5-year survival rates [1]. Only 5.4% and 2.7% of patients survive 5 and 10 years, respectively [2], and the reasons for such extraordinary survival remain elusive.

Early studies categorized GBM patients as Long-Term Survivors (LTS) after 2 or 3 years of survival [3,4], while only a few considered 5-year survivors [[5], [6], [7]]. Most investigations have included patients carrying isocitrate dehydrogenase (*IDH*) mutations, although they represent a different biological entity, as confirmed by the 2021 World Health Organization (WHO) Central Nervous System (CNS) Classification (CNS5) [8].

Many studies highlighted the prognostic significance of younger age at diagnosis, female sex, better performance status and gross total resection [5,6,[9], [10], [11]].

IDH mutations and DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (*MGMT*) promoter (*MGMTp*) methylation are associated with improved GBM overall survival (OS); MGMTp methylation status has been described with a contrasting prognostic role in LTS [12,13]. Co-gain of chromosomes 19 and 20 are reported as favourable prognostic marker [3], while epidermal growth factor receptor *(EGFR)* amplification yielded conflicting results [14,15] with no correlation in LTS [12].

Hypermethylation of glioma cytosine-phosphate-guanine (CpG) island methylator phenotype (G-CIMP) is associated with *IDH* mutation and better outcomes [16]. Searches for specific methylation patterns of LTS versus GBM with standard survival (Short Term Survivors, STS) identified some differences in the two groups [4,[17], [18], [19]], but only one study considered 5-year LTS patients, and findings have not been confirmed [6].

Given this scenario, we believed that further unraveling the alterations responsible for the exceptional GBM survival would aid understanding of tumor biology and help clinicians personalize treatment. As Alleanza Contro il Cancro (ACC) Glioblastoma Working Group, we performed a retrospective study in a large cohort of patients with survival greater than 5-years to detect prognostic factors by comprehensive evaluation including immunohistochemical, genetic and epigenetic profiling.

Section snippets

Patients

Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan (FINCB) coordinated the multicentric retrospective study “Clinical-neuropathological and molecular study in glioblastoma long-term survivors”, involving nine institutions in Italy, as shown in Supplementary Table S1. Ethics Committees of participating institutions approved the study. All procedures were in accordance with Helsinki Declaration and its later amendments.

Main inclusion criteria were adult patients who survived at least 5…

Clinical features of the patient population

The experimental workflow is outlined in Supplementary Fig. S1. A total of 142 GBM-LTS patients surgically resected between January 2000–December 2014 with survival ≥5 years were reviewed and 95 patients with confirmed GBM diagnosis were enrolled [26]. Based on CNS5 WHO, out of 95, 73 were IDH wild-type (GBM-IDHwt) (76.9%), 18 IDH mutant (Astrocytoma-IDHmut, grade 4) (18.9%), by gene sequencing, while in 4 cases IDH status was not assessable for insufficient material.

We focused our analyses on…

Discussion

The percentage of GBM patients achieving 5-year survival is approximately 5% and has not increased in recent decades, despite advances in diagnosis and therapy [1,30]. The small size combined with the heterogeneity of the cohorts investigated made it difficult to identify the clinical and molecular profile of these rare tumors. The main confounding factors were the different definitions of long-term survival (2, 3 and 5 years) and the analysis of tumors with different IDH status according to…

Funding

This work was supported by Italian Ministry of Health (RRC), by Alleanza Contro il Cancro (ACC) Network Project RCR-2021-23671213 and partially by AIRC (IG_21614, to M.T.).…

Declarations ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the FINCB and any adherent centers.…

Consent for publication

Consent for publication was obtained from the participants.…

Data availability

Raw NGS data are deposited in the Sequence Read Archive (SRA) database under submission number SUB13018117 (https://www.ncbi.nlm.nih.gov/sra↗). DNAm raw are deposited in NCBI's Gene Expression Omnibus (GEO; Series accession number GSE230770↗) and are accessible through https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE230770↗.…

CRediT authorship contribution statement

Evelina Miele: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Elena Anghileri:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chiara Calatozzolo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Elisabetta Lazzarini:** Visualization, Methodology, Investigation, Formal analysis. **Sara** …

Declaration of competing interest

The authors declared that have no competing interest.…

Acknowledgements

The authors thank all patients and Claudia Nardini and Veronica Monteferri for the technical support of the methylation analysis, and Biagio De Angelis for gifting U87 cell lines. Luana Abballe was supported by Fondazione Umberto Veronesi. A special thank for the funding organizations: Italian Ministry of Health (RRC), ACC Network Project RCR-2021-23671213 and AIRC (IG_21614, to M.T.).…

Recommended articles

References (47)

C. Hertler *et al.*
Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY brain tumor funders' collaborative consortium (EORTC 1419)
Eur. J. Cancer (2023 Aug)

L. Gately *et al.*
Molecular profile of long-term survivors of glioblastoma: a scoping review of the literature
J. Clin. Neurosci. (2019 Oct)

W. Zhang *et al.*
Genome-wide DNA methylation profiling identifies ALDH1A3 promoter methylation as a prognostic predictor in G-CIMP− primary glioblastoma
Cancer Lett. (2013 Jan)

R.G.W. Verhaak *et al.*
Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1
Cancer Cell (2010 Jan 19)

H.S. Phillips *et al.*
Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis
Cancer Cell (2006 Mar 1)

J.N. Cantrell *et al.*
Progress toward long-term survivors of glioblastoma
Mayo Clin. Proc. (2019 Jul)

M.C. Jin *et al.*
Prognostic factors and treatment patterns in the management of giant cell glioblastoma
World Neurosurg (2019 Aug)

H. Kim *et al.*
Sporadic and Lynch syndrome-associated mismatch repair-deficient brain tumors
Lab. Invest. (2022 Feb)

Q.T. Ostrom *et al.*
CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018

Neuro Oncol. (2021 Oct 5)

H. Gittleman *et al.*
Survivorship in adults with malignant brain and other central nervous system tumor from 2000–2014
Neuro Oncol. (2018 Nov 9)

View more references

Cited by (0)

1 These authors contributed equally to this work.

View full text