Background: Gliomas are the most common type of primary brain tumors with underlying molecular heterogeneity contributing to different treatment responses. Our retrospective study evaluated mutations and biomarkers from a large cohort of glioma patients to identify alterations with therapeutic implications.

Methods: 871 glioma tumor samples (79% WHO grade IV glioblastoma, GBM) were analyzed with a multi-platform approach including sequencing, IHC, FISH/CISH and methylation assay to investigate actionable biomarker alterations. Retrospective data analysis was performed on the complete cohort and molecular subgroups of patients. In the 871 patient samples, mutations in 27 genes were seen. Both common TP53 (93%), IDH1 (22%) and previously unreported mutations in gliomas were observed, including IDH2, A37 and AB1L. Co-mutation of 2 or more genes occurred in 37% of cases. TP53 mutation was suggestive of genetic instability and was frequently associated with other concurrent mutations (p=0.0066). IDH1 mutations were associated with MGMT promoter methylation, low expression of TSG, RRM1 and TOP2A (p from <0.0001 to 0.0038), suggesting different responses to temozolomide, fluorouracil, gemcitabine and etoposide. IDH1 mutation was also associated with TP53 mutations, whereas wild type IDH1 was associated with PTEN mutation (p=0.0309) and showed some association with EGFR mutations (p=0.0543). Distinct biomarker profiles by IHC, FISH and sequencing were also observed when comparing to grade II/III gliomas, suggesting different biology from GBM and thus different treatment implications. 20 GBM patients were identified with pre and post treatment analyses performed (comparative analysis ongoing).

Conclusions: Gliomas exhibit a high degree of molecular heterogeneity as revealed by multi-platform profiling. IDH1 mutation identifies molecular subgroups of patients with different responses to therapeutic agents; while TP53 mutation suggests increased genetic instability. These results highlight the benefits of profiling in consideration of treatment options for glioma patients.

Background: Gliomas are the most common type of primary brain tumors. They are classified as therapeutic agents associated are considered for the full cohort as well as subgroups defined by patient’s tumor grade or their biomarker characteristics into classifying gliomas according to molecular aberrations with the hope of better directing therapy. In our study, multi-platform biomarker analysis was performed on 871 glioma patients who had undergone molecular profiling to investigate actionable biomarker alterations ongoing).

Results of comprehensive molecular profiling of gliomas and the potential therapeutic implications.

Figure 1: Frequencies of biomarker results tested by IHC, FISH/CISH, promoter methylation in the GBM cohort. 85% of 871 glioma patients. The actionable therapies are shown in green (NCCN endorsed agents) and blue (agents off NCCN compendium).

Figure 2: Frequencies of gene mutations. Using a combination of NextG and Sanger sequencing, 27 genes out of 45 tested harbored mutations.

Figure 3: Differentials of biomarker expressions in GBM and grade II/III gliomas. A. Differential expression levels of 23 IHC as well as EGFR (IHC). Asterisks indicate the markers that are significantly associated with tumor grade. (GBM, n=687; Grade II/III gliomas, N=184). B. Differential mutation rates of 27 genes as well as MGMT promoter methylation. Asterisks indicate the markers that are significantly associated with tumor grade. (GBM, N=687; Grade II/III tumors, N=711).

Figure 4: Frequencies co-occurring mutations.(N= number of simultaneous mutations found in one case). The 3 cases with the highest co-mutations are listed with the specific mutations found. The table in red shows that TP53-mutated tumors have a significantly higher chance to harbor additional mutations (75% vs. 52%), suggesting that TP53 mutation is indicative of genetic instability.

Figure 5: Significant biomarker differences in IDH1 mutated vs. IDH1 wild type cases and the associated therapeutic impacts. IDH1 mutation occurs early in gliomagenesis and is an indicator of a more favorable prognosis in glioma. Our data suggest that temozolomide, fluorouracil, gemcitabine and etoposide are potentially more beneficial for GBM patients based on high expression of TOP2A and a high mutation rate of PTEN.

Figure 6: Summary of drug recommendations on glioma tumor profiling reports. (N=818) 90% of cases yielded drug recommendations using multiplatform tumor profiling.

Conclusions

1. Distinct biomarker profiles were observed in WHO grade IV and grade II/III gliomas. The differences included biomarkers measured by IHC, FISH, pyrosequencing (promoter methylation) and NextGen sequencing, associated with potentially different treatment options including chemotherapy as well as targeted therapies.

2. A key mutation is isocitrate-dehydrogenase 1 (IDH1) identifies a patient group potentially more beneficial to patients with IDH1 mutations based on MGMT promoter methylation, low TS and RRM1 expression, TOP2A inhibitors and PTEN. IDH1 wild type patients based on high expression of TOP2A and a high mutation rate of PTEN.

References


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