Precision medicine for glioblastoma

The impact of the precision medicine era has unfortunately not resulted in a substantial improvement in survival of glioblastoma (GBM) patients. Despite extensive molecular knowledge and biomarker subtyping from multiplatform profiling of large numbers of GBMs, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is the only clinical biomarker used to (sometimes) alter treatment for newly diagnosed GBM [1].

One complicating factor is the time expense, and large number of patients required for traditional phases I/II/III drug development associations in a relatively rare and heterogeneous disease such as GBM [2].

In order to address some of these challenges, statisticians, clinical trialists, and regulators have developed and are utilizing novel study designs that can improve efficiency and answer multiple clinical questions within a single clinical trial [3] [4] [5].

Statistical design in a platform study can incorporate standard or Bayesian/adaptive designs in which information gleaned during the operation of the study is used to modify patient randomization and/or continuation or closure of individual substudies [6] [7]

Molecular and clinical heterogeneity critically hinders better treatment outcome for glioblastomas (GBMs); integrative analysis of genomic and epigenomic data may provide useful information for improving personalized medicine. By applying training-validation approach.

Yin et al. identified a novel hypomethylation signature comprising of three CpGs at non-CpG island (CGI) open sea regions for GBMs. The hypomethylation signature consistently predicted poor prognosis of GBMs in a series of discovery and validation datasets. It was demonstrated as an independent prognostic indicator, and showed interrelationships with known molecular marks such as MGMT promoter methylation status, and glioma CpG island methylator phenotype (G-CIMP) or IDH1 mutations. Bioinformatic analysis found that the hypomethylation signature was closely associated with the transcriptional status of an EGFR/VEGFA/ANXA1-centered gene network. The integrative molecular analysis finally revealed that the gene network defined two distinct clinically relevant molecular subtypes reminiscent of different immature neuroglial lineages in GBMs. The novel hypomethylation signature and relevant gene network may provide new insights into prognostic classification, molecular characterization, and treatment development for GBMs [8].

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