MGMT promoter-methylated glioblastoma

- Blood group O attributes to prolonged progression-free survival, overall survival, and 5-year survival in isocitrate dehydrogenase-wildtype glioblastoma patients with MGMT promoter methylation
- Temporal Muscle Thickness as a Prognostic Marker in a Real-Life Cohort of Newly Diagnosed MGMT Promoter Methylated Glioblastoma: A Multicentric Imaging Analysis
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The determination of MGMT status is critical in the glioblastoma management because it helps predict the response to standard chemotherapy, provides prognostic information, allows for more personalized treatment approaches, and aids in the development and testing of new therapies. By tailoring treatment based on MGMT status, healthcare providers can improve outcomes and quality of life for glioblastoma patients.

MGMT (O-6-methylguanine-DNA methyltransferase) promoter-methylated glioblastoma is a specific molecular subtype of glioblastoma

Glioblastoma classifications are based on their genetic and molecular characteristics, and MGMT promoter methylation status is one of the key factors considered in this classification.

The MGMT gene is involved in DNA repair, specifically repairing damage caused by alkylating agents. Methylation of the MGMT gene promoter region is an epigenetic modification that often leads to the silencing or reduced expression of the MGMT gene. In glioblastoma, MGMT promoter methylation is associated with a better response to certain chemotherapeutic agents, particularly alkylating agents like temozolomide.

Here are some key points related to MGMT promoter-methylated glioblastoma:

Response to Temozolomide: Temozolomide is a chemotherapy drug commonly used in the treatment of glioblastoma. MGMT promoter methylation is a predictive biomarker for the response to temozolomide. Tumors with MGMT promoter methylation are more likely to respond to this chemotherapy, leading to improved outcomes.

Prognosis: Patients with MGMT promoter-methylated glioblastoma tend to have a better prognosis

compared to those with unmethylated MGMT promoters. The methylation status of the MGMT promoter is considered a prognostic factor in glioblastoma, influencing the overall survival of patients.

Therapeutic Implications: The presence of MGMT promoter methylation is considered when making treatment decisions for glioblastoma patients. It helps guide the choice of chemotherapy and may influence the overall treatment strategy, including the potential use of temozolomide in the adjuvant setting.

Research and Clinical Trials: Ongoing research is focused on understanding the molecular basis of glioblastoma subtypes, including those with MGMT promoter methylation. Clinical trials may also be designed to explore targeted therapies or combinations of treatments that are specifically effective for MGMT promoter-methylated glioblastomas.

It's important to note that the field of glioblastoma research is dynamic, and advancements in understanding the molecular basis of the disease may lead to further refinements in diagnosis and treatment strategies. Always consult with healthcare professionals for the most up-to-date and personalized information regarding glioblastoma treatment.

O6 methylguanine DNA methyltransferase (MGMT) promoter methylation is a biomarker widely used to predict the sensitivity of IDH-wildtype glioblastoma to temozolomide therapy.

MGMT promoter methylation has predictive value in IDH-mutant glioblastoma, but its cutoff value should be higher than that for IDH-wildtype glioblastoma [1].

Trials aiming at replacing TMZ with targeted agents in unselected patient populations have failed to demonstrate any improvement of survival. Advances in molecular understanding and diagnostic precision enable identification of key genetic alterations in a timely manner and in principle allow treatments with targeted compounds based on molecular markers [2].

Besides a mutated IDH1 status and LOH 1p/19q, methylation of the promoter region of the O6 methylguanine DNA methyltransferase (MGMT) gene has been correlated with favorable outcome in malignant glioma patients.

non-methylated MGMT promotor who are known to have a poor response to alkylating chemotherapy.

O6-methylguanine-DNA methyltransferase (MGMT) has been shown to be an important mechanism underlying resistance to glioma treatment [3].

MGMT expression is largely, but not exclusively [4] controlled via promoter methylation (PM) [5].

The specific measurement of MGMT PM is generally predictive of response and overall survival (OS) in patients with gliomas [6] [7] [8] [9] [10].

Although O(6)-methylguanine DNA methyltransferase (MGMT) promoter methylation status is an important marker for glioblastoma multiforme (Glioblastoma), there is considerable variability in the clinical outcome of patients with similar methylation profles.

In patients with glioblastoma multiforme, the methylation state of the MGMT gene determined whether tumor cells would be responsive to temozolomide; if the promoter was methylated, temozolomide was more effective.

On a clinical level, this translates into a prolonged survival of glioblastoma patients with a methylated MGMT promoter. In addition, MGMT methylation can be used to predict patient survival in clinical prediction models.

For testing of the MGMT promoter methylation status in the clinical setting, DNA-based methods such as methylation-specific polymerase chain reaction (MS-PCR) or pyrosequencing are preferred over immunohistochemical or RNA- based essays.

The O6-methylguanine-DNAmethyltransferase (MGMT) promoter methylation and 1p19q codeletion status can predict sensitivity to chemotherapy and radiation in low- and intermediate-grade gliomas. Thus, these recent advances, which have led to a better understanding of how molecular, genetic, and epigenetic alterations influence the pathogenicity of the different histological grades of gliomas, can lead to better prognostication and may lead to specific targeted surgical interventions and medical therapies [11)].

To what extent improved response reflects low or absent MGMT activity in glioma tissue has not been unequivocally assessed.

Results provide strong support for the hypotheses that MGMT activity promotes alkylator resistance and reflects promoter methylation status in malignant gliomas [12)].

Temozolomide rechallenge is a treatment option for MGMT promoter-methylated Glioblastoma recurrence. Alternative strategies need to be considered for patients with progressive glioblastoma without MGMT promoter methylation [13)].

MGMT promoter methylation and IDH1 mutation were associated with pseudoprogression disease (psPD) and predicted a longer median survival in Glioblastoma patients after TMZ-based chemoradiotherapy. Genetic analyses of the MGMT promoter and IDH1 may allow us to effectively treat Glioblastoma patients [14)].

Analysis

Several methods have been applied to its analysis, with methylation-specific polymerase chain reaction (MSP) the most commonly used for promoter methylation study, while immunohistochemistry (IHC) has become the most frequently used for the detection of MGMT protein expression. Agreement on the best and most reliable technique for evaluating MGMT status remains unsettled.

Protein expression assessed by IHC alone fails to reflect the promoter methylation status of MGMT. Thus, in attempts at clinical diagnosis the two methods seem to select different groups of patients

and should not be used interchangeably [15].

Hypermethylation of the O6 methylguanine DNA methyltransferase (MGMT) gene has been shown to be associated with improved outcome in glioblastoma (Glioblastoma) and may be a predictive marker of sensitivity to alkylating agents. However, the predictive utility of this marker has not been rigorously tested with regard to sensitivity to other therapies, namely radiation.

To address this issue, Rivera et al. assessed MGMT methylation status in a cohort of patients with Glioblastoma who underwent radiation treatment but did not receive chemotherapy as a component of adjuvant treatment. Formalin-fixed, paraffin-embedded tumor samples from 225 patients with newly diagnosed Glioblastoma were analyzed via methylation-specific, quantitative real-time polymerase chain reaction following bisulfite treatment on isolated DNA to assess MGMT promoter methylation status. In patients who received radiotherapy alone following resection, methylation of the MGMT promoter correlated with an improved response to radiotherapy. Unmethylated tumors were twice as likely to progress during radiation treatment. The median time interval between resection and tumor progression of unmethylated tumors was also nearly half that of methylated tumors. Promoter methylation was also found to confer improved overall survival in patients who did not receive adjuvant alkylating chemotherapy. Multivariable analysis demonstrated that methylation status was independent of age, Karnofsky performance score, and extent of resection as a predictor of time to progression and overall survival. Our data suggest that MGMT promoter methylation appears to be a predictive biomarker of radiation response. Since this biomarker has also been shown to predict response to alkylating agents, perhaps MGMT promoter methylation represents a general, favorable prognostic factor in Glioblastoma [16].

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