Towards the definition of a prognostic score based on MGMT methylation status in patients with glioblastoma: do not lose the forest looking at the tree

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Background: Epigenetic variations in the O6-methylguanine-methyltransferase (MGMT) gene had been widely associated with a favorable impact on survival in patients (pts) affected by glioblastoma (GBM). MGMT includes 98 CpG islands (CpGi) and patterns of methylation are rather heterogeneous. Aim of this study is to explore a scoring system based on the gene promoter methylation in order to predict pts’ prognosis.

Materials and methods: We retrospectively analyzed a series of 121 pts with GBM treated at the University Hospital of Udine between 2008 and 2014. The methylation level of CpGIs from 74 to 83 was determined by pyrosequencing. In accordance to previous literature, each island was assigned with 1 point if the corresponding methylation level was higher than 9%. The sum consisted in a score that went from 0 (all CpGs < 9%) to 10 (all CpGs >= 9%). A training set of 75 pts was randomly generated. A threshold capable to detect a favorable outcome (Overall Survival, OS > 24 months) was identified by ROC analysis. The prognostic impact was explored through Cox regression. The results were verified on a validation set of 46 pts.

Results: Median OS and follow-up were 14 and 32.6 months respectively. Among the total population 35% of the pts had a score of 0, while 29% had a score of 10. The score’s prognostic impact was confirmed also by comparison with the methylation mean and median through stepwise Cox regression (p = 0.0002). The threshold identified was 6 (ROC Area = 0.74). On univariate analysis, a score > 6 was associated with a favorable prognosis both in the training and in the validation set (HR 0.42, 95% CI 0.23-0.77, p = 0.0046; HR 0.37, 95%CI 0.18-0.77, p = 0.0078; respectively). This result was confirmed in the whole population by the multivariate analysis (HR 0.34, 95%CI 0.21-0.55, p<0.0001) after adjustment for age (>70 vs ≤ 70 years HR 1.56, 95% CI 0.87-2.78, p = 0.1337), ECOG performance status (0-1 vs 2-3 HR 1.60, 95%CI 0.94-2.73, p = 0.0858) and treatment regimen (RT or CT vs STUPP HR 2.11, 95%CI 1.21-3.67, p = 0.0081). Similar results were observed also in terms of progression free survival (HR 0.46, 95%CI 0.30-0.72, p = 0.0007).

Conclusions: Our study explored a novel scoring system capable to predict GBM pts’ prognosis independently from age, performance status and treatment. Information by combining multiple CpGi and data from each site increased the prognostic value of methylation assessment.

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