rs489693 melanocortin receptor-4 gene polymorphism is associated with the progression-free survival of glioblastoma patients treated with concomitant radio-chemotherapy

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Background. Glioblastoma (GBM) accounts for approximately 50% of all glioma and among these tumors, are the most malignant. The cells of origin of glioma are still undefined, but the most putative target cells include astrocytes, neural stem cells, and oligodendrocyte precursor cells (Jiang and Uhrbom, 2012). The current standard of care for patients with newly diagnosed GBM includes temozolomide and radiotherapy (Stupp et al., 2009). Melanocortins are peptides with well-recognized anti-inflammatory and neuroprotective activity. Of the five known melanocortin receptors (MCRs), only subtype 4 is present in astrocytes and it is expressed predominantly in the brain (Caruso et al., 2013). No data are currently available on MC4R gene polymorphisms and gliomas or their relationship with radiotherapy or chemotherapy.
Aim. Given the association of MC4R with antiinflammatory activity, neuroprotection, induction of neural stem/progenitor cell proliferation in brain hypoxia, and prevention of astrocyte apoptosis (Giuliani et al., 2012), the aim of this study was to retrospectively evaluate the possible prognostic/predictive role of the MC4R SNPs on GBM therapy.
Methods. Sixty-one patients with a proven diagnosis of GBM, ECOG PS 0-2, age>18 years, and treated with radiotherapy and temozolomide were enrolled. Blood samples (3 ml) were collected in EDTA tubes and stored at -80°C. Genomic DNA was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). *MC4R* gene SNPs (rs17782313, rs489693, rs8087522, rs17700633) were analyzed; the allelic discrimination was performed using an ABI PRISM 7900 SDS (Applied Biosystems, Carlsbad, CA, USA) and with validated TaqMan® SNP genotyping assays (Applied Biosystems). PCR reactions were carried out according to the manufacturer's protocol. Kaplan Meier curves were performed for statistical association with genotypes. A *P* value <0.0125 (Bonferroni's correction) was considered significant. The study has been approved by the Comitato Etico di Area Vasta Nord Ovest (CEAVNO) prot. n. 17013.
Results. Fifty-six patients were clinically evaluated. The median progression-free survival (PFS) and median overall survival (OS) of these patients were 10.8 months and 23 months, respectively. The distribution of genotypes in the 56 patients did not deviate from Hardy–Weinberg equilibrium. A relevant finding of our study was the identification of a MC4R genotype that was significantly associated with PFS. Indeed, with regard to PFS, patients harbouring the rs489693 AA genotype had a median PFS of 3 months whereas patients with AC/CC genotypes had a median PFS of 13.7 months (*P*=0.0088). Interestingly, the rs489693 AA patients also had a lower median OS, even though the difference was not statistically significant as compared with the median OS of the AC/CC genotypes (15.6 *vs.* 24.6 months, respectively, *P* =0.274). No significant differences in PFS and OS for the other genotypes of the investigated MC4R polymorphisms were found.
Conclusion. The rs489693 AA genotype is significantly associated with a shorter PFS in GBM patients treated with radiotherapy and temozolomide schedule. The present pharmacogenetic, retrospective, pilot study may represent the stimulus to prospectively investigate the role of rs489693 MC4R polymorphism as a predictive pharmacogenetic marker of GBM radio-chemotherapy.

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