**Role of circulating tumor DNA in personalised medicine**

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Glioblastoma (GBM) is the most diffuse and aggressive primary brain tumor in adults and its current therapeutic options are still limited (1,2). The genomic characterization of tumors has become crucial for the diagnosis, treatment and response-monitoring, however, in GBM patients surgery and postoperative radio-chemotherapy with temozolomide (TMZ) still represent the standard of care, with a survival averages extended by 2.5 months only in the last 10 years (1,3).

Primary and secondary GBMs are characterized by different aggressiveness, overall survival (OS) and response to radio-chemotherapy treatments (4). In 1996, different genetic alterations in tumor tissue were reported in these two different groups of GBMs and, in 2008, the isocitrate dehydrogenase 1 (IDH-1) gene mutations were identified as prognostic molecular biomarker of low grade glioma and, thereby, of secondary GBMs, which represent their clinical and pathological evolution. Vice versa, IDH-1 wild type has been considered a signature of primary GBM, identifying patients with a worst prognosis (5,6). Thereby, several authors reported that after surgery and radio-chemotherapy, patients with IDH-1 mutant GBM showed a mean OS greater than 25 months, whereas, patients with IDH-1 wild type GBM just a little higher than 10 months (7,8).

Recently, given the reported observation of spatial and temporal tumor heterogeneity, a new approach to tumor heterogeneity has been developed in many solid tumors, including GMB, with the analysis of DNA somatic mutations on circulating tumor DNA (ctDNA) in plasma (9,10). However, the ctDNA analysis of brain malignancies has revealed very low levels (if not the absence) of tumor DNA in plasma. The blood-brain barrier (BBB) is probably the responsible for the few release of tumor DNA from the brain to the peripheral circulation. However, while there is evidence that the integrity of the BBB in GBM patients is highly compromised due to the local therapies (11-13), it is possible that this breakdown in the BBB could allow GBM-DNA releasing from the tumor into the peripheral blood. In the future this might allow not only serologic diagnosis of GBM, but perhaps other characterization of intracranial neoplasms including factors suggestive of better response to specific/targeted therapies. It could also be studied prospectively for possible use in detecting post-resection tumor recurrence and distinguishing recurrence from post-radiation necrosis.

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