Transcriptional changes induced by bevacizumab combination therapy in responding and non-responding recurrent glioblastoma patients

Background: Bevacizumab combined with chemotherapy produces clinical durable response in 25-30% of recurrent glioblastoma patients. This group of patients has shown improved survival and quality of life. The aim of this study was to investigate changes in gene expression associated with response and resistance to bevacizumab combination therapy. Methods: Recurrent glioblastoma patients who had biomarker-accessible tumor tissue surgically removed both before bevacizumab treatment and at time of progression were included. Patients were grouped into responders (n = 7) and non-responders (n = 14). Gene expression profiling of formalin-fixed paraffin-embedded tumor tissue was performed using RNA-sequencing. Results: By comparing pretreatment samples of responders with those of non-responders no significant difference was observed. In a paired comparison analysis of pre- and posttreatment samples of non-responders 1 gene was significantly differentially expressed. In responders, this approach revealed 256 significantly differentially expressed genes (72 down-and 184 up-regulated genes at the time of progression). Genes differentially expressed in responders revealed a shift towards a more proneural and less mesenchymal phenotype at the time of progression. Conclusions: Bevacizumab combination treatment demonstrated a significant impact on the transcriptional changes in responders; but only minimal changes in non-responders. This suggests that non-responding glioblastomas progress chaotically without following distinct gene expression changes while responding tumors adaptively respond or progress by means of the same transcriptional changes. In conclusion, we hypothesize that the identified gene expression changes of responding tumors are associated to bevacizumab response or resistance mechanisms.