176 IMMUNE MICROENVIRONMENT OF PRIMARY VERSUS METASTATIC MELANOMA OF THE BRAIN

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Background Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of melanoma resulting in improved clinical outcomes, however approximately 50% of patients ultimately develop resistance and progress on ICPI. Significant clinical morbidity is encountered when melanomas metastasize rapidly, including spread to the brain and other sites. Understanding the immune evasion mechanisms is important in guiding effective immunotherapy selection in metastatic melanoma. In this study, we investigated the differences in the immune landscape between primary and metastatic melanoma of the brain and other predominant metastatic sites.

Methods A cohort of 426 melanoma samples was evaluated by comprehensive genomic and immune profiling, including PD-L1 IHC, TMB and expression of 395 immune genes. Tumor specimens were classified as primary skin (PS) or by their site of metastasis including lymph node (LN), brain (BM), soft tissue (STM), lung (LuM), or liver (LiM). LN samples were used as positive controls due to expected strong inflammation. PD-L1 (TPS $\geq$1%) and TMB (high $\geq$10 Mut/Mb) were obtained by IHC and DNA sequencing, respectively. Gene expression signatures of tumor inflammation (TIGS), cell proliferation (CP; poor<=33; 33>moderate<66; high>=66) and expression of *LAG3*, *TIGIT* and *TIM3* were determined by RNA-sequencing. We used chi-square and Wilcoxon rank-sum tests to determine the association of specimen sites to genomic and immune correlates.

Results The median age of diagnosis was 68 years, with 58% of patients being male. Specimen sites distributions were PS=117 (27%), LN=87 (20%), STM=55 (13%), LuM=40 (9.4%), LiM=31 (7.3%), BM=27 (6.3%), other sites = 69 (16%). BM had significantly reduced inflammation score (22.97) when compared to PS, LN, STM, and LuM (44.7–56.98; $p<0.01$). Most groups had a higher proportion of moderate CP score except for LiM, having mostly poor CP (74%, $p<0.001$). BM showed higher median TMB (32.95) compared to LN and STM (11.7, 7.8; $p<0.05$). BM showed lower expression ($p<0.05$) of *LAG3*, *TIM3*, and *TIGIT* when compared to LN, STM, LuM, and PS.

Conclusions Melanoma BMs have a less robust immune response compared to PS, LN and other metastatic sites, suggesting a lower degree immune cell infiltration resulting in an overall reduced expression of ICPI targets. These findings support the clinical challenge that melanoma BMs often do not have durable responses to systemic ICIs and targeted therapies alone. Combination treatments of ICIs with local radiation therapy may be a promising therapeutic approach in melanoma BM, resulting in synergistic and abscopal effects on immune system activation.

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