study aimed to determine whether health-related quality of life (HRQoL) can be maintained during progression-free time, and factors associated with HRQoL deterioration in this period. MATERIAL AND METHODS: We included longitudinal HRQoL data from previously published clinical trials in glioma. The percentage of patients with stable HRQoL until progression was determined per scale and at the individual patient level (i.e. considering all scales simultaneously). We assessed time to a clinically relevant deterioration in HRQoL, expressed in deterioration-free survival and time-to-deterioration (the first including progression as an event). We also determined the association between sociodemographic and clinical factors and HRQoL deterioration in the progression-free period. RESULTS: 5539 patients with at least baseline HRQoL scores had a median time from randomization to progression of 7.6 months. Between 9%-29% of the patients deteriorated before disease progression on the evaluated HRQoL scales. When considering all scales simultaneously, 47% of patients deteriorated on ≥1 scale. Median deterioration-free survival period ranged between 3.8–5.4 months, and median time-to-deterioration between 8.2–11.9 months. For most scales, only poor performance status was independently associated with clinically relevant HRQoL deterioration in the progression-free period. CONCLUSION: HRQoL was maintained in only 53% of patients in their progression-free period, and treatment was not independently associated with this deterioration in HRQoL. Routine monitoring of the patients' functioning and well-being during the entire disease course is therefore important, so that interventions can be initiated when problems are signalled.

KS01 THE DIFFERENTIAL IMMUNE LANDSCAPE IN BETWEEN PRIMARY AND SECONDARY BRAIN TUMORS

KS01.3.A TUMORAL MHC CLASS II EXPRESSION IN GLIOMAS DRIVES T CELL EXHAUSTION

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BACKGROUND: Neoepitopes are presented on major histocompatibility class II (MHCII) molecules. In glioma, for instance, the recurrent driver mutation IDH1R132H was shown to bear an MHCII-restricted epitope in preclinical and clinical vaccine studies. The general relevance of MHCII expression in glioma for antitumor immunity, however, remains unknown. Here we evaluate stromal and tumoral MHCII expression, functionality, and its association with survival in gliomas. MATERIAL AND METHODS: Immunostaining of human glioma tissues was used to identify tumoral, endothelial, and microglial MHCII expression and to enumerate T cell infiltrates. To gain insights into tumoral MHCII expression, bulk transcriptomic data from TCGA and single-cell transcriptomic data from publicly available datasets were analyzed. MHC ligandome analyses of an MHCII$^+$ glioma cell line and human glioma tissues were used to determine the functionality of MHCII *in vitro* and *ex vivo*. Functional *in vitro* co-culture assays with an HLA-DR-matched tetanus toxoid (TT) epitope-overexpressing glioma cell line and *in vitro*-expanded TT-reactive T cells from healthy donors were used to examine direct target recognition by T helper cells. CRISPR-Cas9-mediated knockout of MHCII in preclinical hypermutant glioblastoma cell line GL261 was employed to further validate the consequences of tumoral MHCII expression and to probe potential clinical intervention with existing therapies. RESULTS: MHCII is expressed in the majority of gliomas and associated with increased infiltration of T cells. In 10% of the analyzed glioma tissues and a subset of single cells, tumoral MHCII expression is detected. Clinical and transcriptomic data reveal that tumoral MHCII is associated with poor prognosis, cytokine responses, immune inhibition and T cell differentiation. Ligandome analyses evidence presentation of peptides by MHCII molecules on glioma cells. In *in vitro* assays, TT-reactive T helper cells specifically produce IFNg when co-cultured with MHCII$^+$ glioma cells upon the presence of co-stimulation. In agreement with the clinical data, preclinical murine models demonstrate that tumoral MHCII expression leads to reduced survival. Co-culture assay shows that tumoral MHCII results in upregulation of PD-1 on T helper cells antigen-specifically. Concordantly, immune checkpoint blockade (ICB) therapy slows the disease progression of mice carrying MHCII$^+$ tumors. CONCLUSION: MHCII is expressed in gliomas by a subset of tumor cells. Although tumoral MHCII is functional, it is associated with poor survival in both clinical data and preclinical models. T cell exhaustion induced by tumoral MHCII expression can, in part, be overcome by ICB *in vivo*. Further experiments are required to decipher tumor cell intrinsic and microenvironmental consequences of tumoral MHCII expression.

KS01.4.A NK CELLS AS KEY ORCHESTRATORS IN MEDIATING THE ANTI-TUMOUR RESPONSE TO IMMUNE CHECKPOINT BLOCKADE IN MELANOMA BRAIN METASTASES

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BACKGROUND: Brain metastases (BrM) are an unmet clinical need with poor prognosis. 60% of melanoma patients develop BrM. BrM are strongly understudied due to frequent exclusion from clinical trials, and hence treatment options commonly lag behind. Antibodies targeting the immune-inhibitory receptors cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have demonstrated efficacy against melanoma BrM. Despite this, therapeutic responses are highly variable, and it is unknown why therapy fails in a high proportion of patients. Improved therapeutic strategies require a thorough understanding of potentially exploitable mechanisms of therapeutic efficacy. Our data previously implicated different immune cells, foremost CD8+ T cells, but also NK cells, in the intracranial efficacy and enhanced survival benefit of immune checkpoint blockade (ICB). Our aim here is to investigate the role of NK cells in mediating the response to ICB in melanoma BrM. MATERIAL AND METHODS: To study the role of NK cells in the response to ICB in melanoma BrM, a tumour transplantation model of B16 melanoma with simultaneous extracranial (i.e., flank) and brain tumours in C57BL/6 mice was utilised. NK cells were depleted through administration of anti-asialo-GM1 NK cell-depleting antibodies. Confirmation of NK cell depletion and quantification of intratumoral immune cell populations was performed using flow cytometry. Intratumoral gene expression of key chemokines and immune mediator genes was assessed using RT-qPCR and mRNA-seq. RESULTS: Highly variable response to ICB with respect to intratumoral accumulation of CD8+ T cells allowed separation of mice into responders and non-responders and revealed genes and pathways associated with response to ICB. NK cell depletion reversed the ICB-mediated increase in the accumulation of CD8+ T cells and significantly reduced the expression of genes associated with response in intracranial and extracranial tumours. The ICB-mediated significant increase in gene expression of various chemokines (i.e., Cxcl9/10) and immune mediators (i.e., Ifng, Prf1 and Gzmb) was significantly abrogated upon NK cell depletion. CONCLUSION: NK cells play a critical role in the underlying mechanisms of ICB efficacy through their modulation of the tumour microenvironment and enhancement of CD8+ T cell accumulation in intracranial tumours. Targeting of NK cells may allow potentiation of ICB therapy in the brain, as well as at extracranial sites.

KS01.5.A ALLERGIC AIRWAY INFLAMMATION IMPACTS TUMOR TAKE AND DELAYS EXPERIMENTAL GLIOBLASTOMA PROGRESSION

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BACKGROUND: Numerous epidemiological studies have highlighted the protective role of immunoglobulin E-mediated allergic diseases on glioblastoma (GBM) susceptibility and prognosis. However, the mechanistic explanations behind these phenomena remain unexplored. Our objective was to set up a preclinical model and investigate the mechanisms underlying such protection to improve our understanding of the crosstalk between immune system and brain tumor development. MATERIAL AND METHODS: A mouse model of allergic airway inflammation (AAI) induced by repeated nasal instillation of House Dust Mite extract was initiated before intracranial implantation of GL261 glioma cells, in both immunocompetent (C57BL/6) and immunodeficient (RAG-KO) mice. Tumor take and tumor growth were monitored by MRI. Central (microglia) and peripheral (spleen, bone marrow) immune cells were characterized by flow cytometry. The response of microglia was further assessed by RNA sequencing. Impact of candidate genes on patient survival was characterized by Cox regression analysis using data from TCGA and CGGA. RESULTS: Following AAI induction in C57BL/6 mice, engraftment of GL261 cells in the brain was delayed and tumor growth rate