(33-53) (R-MBVP)) (HR 0.73, 95% CI 0.52-1.02, p=0.07). 80 patients were still alive. Overall survival (OS) at 5 years for MBVP and R-MBVP was 49% (39-59) and 53% (43-63) respectively. A total of 111 patients had progression or relapse, 63 after MBVP and 48 after R-MBVP. 79% of these patients received further treatment. The median OS after progression/relapse was 9.7 months (5.9-19.9) in the MBVP arm, and 6.1 months (2.4-13.1) in the R-MBVP arm (HR 1.25, 95% CI 0.83-1.87, p=0.29). 119 patients died, 64 in the MBVP arm and 55 in the R-MBVP arm. Causes of death were PCNSL in 69% of the patients (both arms), complication of treatment (6% vs 5%), secondary malignancy (5% vs 2%) and other or unknown causes (20% vs 24%). Age was the strongest prognostic factor for EFS, PFS and OS in multivariate analysis. CONCLUSION: in the modified-ITT population we found no statistically significant benefit of the addition of rituximab to MBVP on EFS, PFS and OS in patients with PCNSL, even after a long follow-up of median 82 months. Therefore, the results of this study do not support the use of rituximab with MBVP in the treatment of primary CNS lymphoma.

OS03.7.A. CLINICAL CHARACTERISTICS, TREATMENT AND LONG-TERM OUTCOME OF PATIENTS WITH BRAIN METASTASES FROM THYROID CANCER - AN ANALYSIS OF THE VIENNA BRAIN METASTASIS REGISTRY

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BACKGROUND: The incidence of brain metastases (BM) in patients with thyroid cancer (TC) depends on the histological subtype. About 1% of patients with differentiated (DTC), 3% with medullary (MTC) and up to 10% with anaplastic thyroid cancer (ATC) develop BM. The diagnosis of BM drastically worsens the prognosis of TC. Given the rare incidence, little is known about the presentation and outcome of this cohort. MATERIAL AND METHODS: Patients with a histologically verified diagnosis of TC and BM were identified from the Vienna Brain Metastasis Registry, a comprehensive database managed by the Division of Oncology, Medical University of Vienna, including patients with cerebral metastasis since 1990. Data were obtained from medical records comprising clinicopathological features, treatment, BM-specific characteristics and outcome. RESULTS: 20/6074 patients included in the registry had a diagnosis of TC and radiologically verified BM. 13/20 (65%) were female and the median age at diagnosis of TC and manifestation of BM was 56 years (range 21-75) and 68 years (range 45-75), respectively. In terms of histology, 18/20 (90%) had DTC, one MTC and one ATC. Interestingly, 10/18 DTC presented with follicular histology which underlines the more aggressive course of this rare subtype. 6/20 (30%) had BM at primary diagnosis (DTC n=5, ATC n=1), while the remaining developed BM during follow-up. The median time to diagnosis of BM was 2.6 years for DTC (range 0-42), 22 years in the MTC patient and 2 months for ATC. Regarding BM-specific characteristics, all but one patient had symptoms due to BM (neurological deficits n=11, increased intracranial pressure n=5, seizures n=3). Most patients (13/20) had a singular BM, commonly located in the left hemisphere (8/13), and only one had more than three BMs. Upfront treatment for BM was local therapy (resection n=9, stereotactic radiosurgery n=7, whole brain radiotherapy n=3); one patient received supportive care only. The median overall survival (mOS) from diagnosis of TC was 6 years for DTC (range 2.5 months-42 years), 33 years for the MTC and 9 months for the ATC. The mOS from diagnosis of BM was 14 months for DTC (1.8 months-16 years), 22 years for the MTC and 3 months for the ATC. CONCLUSION: Few patients with TC develop BM, which present commonly as single lesion. While in general BM constitute a poor prognostic factor, individual patients experience long-term survival following local therapy. More information about the optimal management of BM in TC is needed to enable guideline recommendations.

OS05 DISSECTING AND TARGETING PRO-TUMORAL STATES OF THE MICROENVIRONMENT

OS05.4.A. SINGLE-CELL CHARACTERIZATION OF HUMAN GBM REVEALS REGIONAL DIFFERENCES IN TUMOR-INFILTRATING LEUKOCYTE ACTIVATION

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BACKGROUND: Clinical trials of systemic T cell checkpoint blockade in GBM patients showed only disappointing results. This may be attributed in part to the immunosuppressive components of the GBM immune tumor microenvironment (iTME). Therefore, major efforts have been undertaken to describe the GBM iTME on a single cell level. However, human data on the composition of the iTME in different tumor regions (contrast enhancing tumor center versus peripheral infiltration zone) remain scarce. MATERIAL AND METHODS: Here, we performed high-depth single-cell RNA sequencing (scRNA-seq) on patient-matched biopsies from tumor center and the peripheral infiltration zone of five primary GBM patients. Additionally, peripheral blood mononuclear cells (PBMC) of the same patients were included in the analysis to explore the transcriptional changes occurring during tumor infiltration of circulating immune cells. Main findings of the transcriptional analysis were confirmed by flow cytometry. RESULTS: Through analysis of > 45'000 cells, we revealed a distinct regional transcriptional profile of microglia (MG) and monocyte-derived macrophages (MdM), a non-reactive/exhausted MG subcluster in the GBM iTME and an impaired interferon-response signature in the tumor-peripheral cytotoxic cell compartment. Comparing $CD8^+$ T cells from the tumor periphery to PBMC-derived $CD8^+$ T cells of the same patient revealed $CX3CR1^{high}$ and $CX3CR1^{int}$ $CD8^+$ T cells with effector and memory phenotype, respectively, enriched in the PBMC but lacking in the tumor periphery. Tumor peripheral $CD8^+$ T cells shared features with tissue-resident memory $CD8^+$ T cells with exhausted effector functions. CONCLUSION: Our analysis provides a large-scale dissection of GBM-associated cell types complemented by patient-matched PBMCs, serving as a high dimensional reference map of the human GBM iTME.

OS05.5.A. GLIOBLASTOMA-INSTRUCTED MICROGLIA TRANSIT TO HETEROGENEOUS PHENOTYPIC STATES WITH DENDRITIC CELL-LIKE FEATURES IN PATIENT TUMORS AND PATIENT-DERIVED ORTHOTOPIC XENOGRAFTS

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BACKGROUND: A major contributing factor to Glioblastoma (GBM) development and progression is its ability to evade the immune system by creating an immune-suppressive tumor microenvironment (TME). GBM-associated myeloid cells, including resident microglia, macrophages and other peripheral immune cells are generally geared towards tumor-supportive roles. It is however unclear whether such recruited myeloid cells are phenotypically and functionally identical. Here, we aim to understand the heterogeneity of the GBM TME, using an unbiased, marker-free approach to systematically characterize cell type identities at the molecular and functional levels. MATERIAL AND METHODS: We applied single-cell RNA-sequencing, multicolor flow cytometry, immunohistochemical analyses and functional studies to examine the heterogeneous TME instructed by GBM cells. GBM patient-derived orthotopic xenografts (PDOXs) representing different tumor phenotypes were compared to glioma mouse GL261 model and patient tumors. RESULTS: We show that PDOX models recapitulate major components of the TME found in human GBM. Human GBM cells reciprocally interact with mouse cells to create a GBM-specific TME. The most prominent transcriptomic adaptations are found in tumor-associated macrophages (TAMs), which are largely of microglial origin. We reveal inter-patient heterogeneity of TAMs and identify key signatures of distinct phenotypic states within the microglia-derived TAMs across distinct GBM landscapes. GBM-educated microglia adapt expression of genes involved in immunosuppression, migration, phagocytosis and antigen presentation, indicating functional cross-talk with GBM cells. We identify novel phenotypic states with astrocytic and endothelial-like features. Identified gene signatures and phenotypic states are confirmed in GBM patient tumor tissue. Finally we show that temozolomide treatment leads to transcriptomic adaptation of not only the GBM tumor cells but also adjacent TME components. CONCLUSION: Our data provide insights into the phenotypic adaptation of the heterogeneous TME instructed by GBM tumor. We confirm a crucial role of microglia in supporting the immunosuppressive TME and show that PDOXs allow to monitor the highly plastic GBM ecosystem and its phenotypic adaptations upon treatment. This work further confirms the clinical relevance of PDOX avatars for testing novel therapeutics including modalities designed to target the myeloid compartment.

OS05.6.A. MODIFICATION OF THE TUMOR MICROENVIRONMENT IN PATIENTS WITH GLIOBLASTOMA USING AUTOLOGOUS, GENETICALLY MODIFIED, HEMATOPOIETIC STEM CELL-BASED THERAPY: THE TEM-GBM STUDY (NCT03866109)

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BACKGROUND: Bone marrow-derived macrophages account for substantial GBM tumor volume and contribute to the local inflammatory tumor microenvironment, disease progression and treatment response. MATERIAL AND METHODS: We have developed a genetically modified, autologous hematopoietic stem cell-based platform designed to deliver Interferon-alpha (IFNa), thanks to a transcriptional and post-transcriptional control mechanism mediated by miRNA target sequences, specifically into the tumor microenvironment via Tie-2 expressing monocytes (Temferon). RESULTS: As of Feb 2022, 3 escalating doses of Temferon (from 0.5 to $2.0x10^6$/kg) were tested across 15 patients with newly diagnosed, unmethylated MGMT glioblastoma (GBM) assigned to 5 cohorts. The duration of follow-up from surgery is 6 - 28 mo (2 - 25 mo after Temferon). To date, no dose limiting toxicities have been identified. As expected, one month after the administration of the highest tested dose, the hematopoietic system of Temferon-treated patients was composed of up to 30% of CD14+ genetically modified cells, as determined by the presence of vector genomes in the DNA in peripheral blood and bone marrow cells. Temferon-derived progeny persisted, albeit at lower levels, up to 18 months (longest time of analysis). Despite the substantial proportion of engineered cells, very low median concentrations of IFNα were detected in the plasma (D+30, 5.9; D+90, 8.8pg/mL) and in the CSF (D+30, 1.5; D+90, 2.4pg/mL), indicating tight regulation of transgene expression. SAEs were mostly attributed to conditioning chemotherapy (e.g. infections) or disease progression (e.g. seizures). 1 SUSAR (persistent GGT elevation) has occurred. Median OS is 15 mo from surgery (range 6.1-28.4 mo; 10.8 mo post Temferon). Of the 15 pts treated so far, 4 pts belonging to low dose cohorts underwent 2nd surgery. Homing of transduced cells from BM to the tumor site was demonstrated by the presence of gene-marked cells in the specimens collected from 3 of the 4 analyzed pts. Single-cell RNA seq performed on CD45+ cells purified from the TME of Temferon-treated pts compared to recurrent tumors belonging to GBM pts treated as per the current standard of care, highlighted a Temferon signature defined by the induction of markers of IFNa responses and macrophage repolarization. Potential long-term benefit with Temferon was identified in a patient from cohort 3, who had disease progression at D+120 with two distant enhancing lesions, and increased tumor necrosis. One year following Temferon, with no 2nd line therapy added, there was approximately 40% reduction in enhancing tumor volume compared to D+180 with a stable clinical and imaging picture thereafter. CONCLUSION: The results provide initial evidence of Temferon's potential to modulate the TME of GBM patients, and anecdotal evidence for long lasting effects of Temferon in prevention of disease progression.

OS06 QUALITY OF LIFE

OS06.5.A. INVESTIGATING SAFETY AND EFFICACY OF TTFIELDS PRIOR AND CONCOMITANT TO RADIOTHERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA - THE PRICOTTF PHASE I/II TRIAL

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BACKGROUND: The EF-14 phase III trial demonstrated improved survival for patients with newly diagnosed glioblastoma (nGBM) when TTFields therapy was added to adjuvant temozolomide chemotherapy. TTFields at 200 kHz are applied to the tumor utilizing arrays on the patients' scalp. In preclinical studies, a synergistic inhibiting effect on glioblastoma cell proliferation was found for the combination of TTFields and radiotherapy. Based on these findings, we conduct the phase I/II PriCoTTF trial in adult nGBM patients to investigate the safety and efficacy of TTFields therapy initiated prior and concomitant to radiochemotherapy. MATERIAL AND METHODS: Per study protocol, TTFields therapy is initiated following surgery and completed wound healing. Continuing throughout radiochemotherapy and adjuvant chemotherapy, TTFields therapy is used for approximately 9 months in total with TTFields rechallenge allowed at recurrence. Radiotherapy is conducted with arrays applied on the patients' scalp. A total recruitment of 33 patients was sought, with 20 patients in arm A receiving normo-fractionated radiotherapy, and 13 elderly patients in arm B receiving hypo-fractionated radiotherapy. Safety and tolerance are the study's primary endpoint, analyzed by a selection of pre-specified treatment-limiting toxicities (TLTs). RESULTS: A total of 33 patients have been enrolled. Patients' characteristics were mostly typical for glioblastoma, except for a rather low fraction of patients with gross total resection (GTR, 22.5%). The distribution of adverse events of common toxicity criteria (CTC) grade 3 or higher was comparable to that of established glioblastoma trials. Notably, skin toxicity of CTC grade 3 or higher was quite uncommon (n=2, 6%). As no patient developed TLTs, the study's primary endpoint was met. Median TTFields treatment duration was 8.4 months. Overall survival data was not mature enough (event rate 48%) to allow for a definite conclusion. Notably, on multivariable Cox regression, the number of days with TTFields adherence of more than 23 hours was independently associated with overall survival (HR 0.96, 95% confidence interval 0.93 - 0.99, p=0.008). CONCLUSION: The PriCoTTF trial met its primary endpoint indicating that combined TTFields and radiotherapy is safe and well tolerated. High-grade skin toxicity was quite uncommon and the patients with high TTFields adherence seem to perform particularly well. An extended follow-up is required to provide first estimates regarding putative efficacy. At that point in time, the reduced overall TTFields duration and fraction of patients with GTR need to be factored in.

OS06.6.A. REAL-WORLD PATTERN OF CARE STUDY ON GLIOBLASTOMA IN THE AUSTRIAN POPULATION. FINAL RESULTS FROM 2014-2020.

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BACKGROUND: The Austrian ABTR-SANO Glioblastoma Registry is the first population-based assessment of patterns of care for patients with Glioblastoma across Austrian healthcare institutions. The primary aim is to assess the real world effectiveness of administered therapies. MATERIAL AND METHODS: Clinical data are collected via a common web-based IT platform "ABTR-SANO Net" since 2014. The database and the ongoing evaluation of clinical parameters, as well as interims analysis are provided in cooperation with a review board. First Outcome analysis, including patients from 2014-2020, was performed at the end of 2021. RESULTS: Eleven centers across Austria are involved, and the data of 1416 patients (m/f ratio: 1,35, median age: 66 years) were recently analyzed in detail. Age, extent of resection, as well as ECOG was associated with improved survival. Methylated MGMT Status also showed a moderate survival benefit. Patients with re-resection and re-radiation also exhibited improved survival, which however may be attributed to a selection bias.Second line treatment manly comprised of antiangiogenic treatment, followed by alkylated agents, re-radiation and re-surgery. Median overall survival of all patients was 344 days and clearly age dependent (best for <50 years, worse for>80 years). CONCLUSION: This is the first population based outcome analysis of Glioblastoma in Austria. Results regarding prognostic markers and outcome are mostly comparable with international data. Robust population based data are important in order to monitor quality of health care, and to match the data with results from clinical studies.