versus 7.0 months [95%CI: 6.1–8.3]; p=0.0003) and patients with <5 BM versus ≥5 BM (12.49 months [95%CI: 10.52–16.03] versus 5.48 months [95%CI: 4.2–6.8]; p<0.0001). Prognostic multivariable modeling significantly associated shortened OS independently with leptomeningeal dissemination (p<0.0001), >5 BM at diagnosis (p<0.0001), MBM diagnosis year 2010–2014 (p=0.0007), immunotherapy treatment prior to BM diagnosis (p=0.02), and extracranial disease presence (p=0.03). CNS-directed treatment modalities associated with BM number, dominant BM size, presenting symptoms, diagnosis year, and extracranial disease presence. Multivariable analysis demonstrated improved survival for patients that underwent craniotomy (p=0.01). CONCLUSIONS: MBM prognosis has improved in the period following targeted and immunotherapy introduction, and even within the last 5 years of this study. Improving survival reflects and may influence the willingness to use aggressive multimodality treatment for MBM.

19. PLEKHA5 REGULATES TUMOR GROWTH IN METASTATIC MELANOMA

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Understanding the mechanisms behind melanoma brain metastasis, a disease that continues to portend a poor prognosis, will lead to the identification and development of novel drug targets. We previously identified PLEKHA5, a gene involved in brain development, as a novel molecule implicated in melanoma brain metastasis. Our aim was to further characterize the function of this protein in brain-tropic melanoma. We established stable loss- and gain-of-function cell lines to explore the underlying mechanisms of PLEKHA5-mediated tumor growth. The effect of PLEKHA5 expression silencing on proliferation and tumor growth was assessed using both in vitro systems and xenograft models of brain-tropic melanomas, respectively. The clinical relevance of PLEKHA5 dysregulation in brain metastasis was also investigated in two unique cohorts of melanoma patients with cerebrotropic disease and included analysis of matched cranial and extra-cranial specimens. Knock-down of PLEKHA5 in brain-tropic melanoma cells negatively regulated cell proliferation by inhibiting G1 to S cell cycle transition. This coincided with up-regulation of PDCD4, p21, and p27, as well as the downregulation of pRb protein, involved in the regulation of cell cycle. Conversely, the ectopic re-expression of PLEKHA5 had an inverse effect. Subcutaneous and direct cranial injections of PLEKHA5 knock-down cells in nude mice significantly inhibited tumor growth, while its overexpression upregulated the growth of tumors. This reduction in tumor growth in vivo might be attributed to decreased phosphorylation of Akt (S473) and mTOR (S2448), key mediators for tumor growth and survival. Our results demonstrate the role of PLEKHA5 as a mediator of melanoma brain metastasis. Our findings highlight the significance of PLEKHA5 as a possible regulator of cell cycle transition via crosstalk with the ubiquitin-proteasome and PI3K/AKT/mTOR signaling pathways, driving the proliferation and growth of brain-tropic melanomas. Our studies suggest that PLEKHA5 targeting should be further investigated for melanoma brain metastasis patient population.

20. MELANOMA CELL INTRINSIC GABAA RECEPTOR ENHANCEMENT POTENTIATES RADIATION AND IMMUNE CHECKPOINT INHIBITOR RESPONSE BY PROMOTING DIRECT AND T CELL-MEDIATED ANTI-TUMOR ACTIVITY

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Most metastatic melanoma patients exhibit poor and variable response to radiotherapy and targeted therapies, including immune checkpoint inhibitors. There is a need for therapeutics that can potentiate existing treatments to positively impact clinical outcomes of metastatic melanoma patients. We reanalyzed melanoma TCGA transcriptomes and identified, as linked to previously defined molecular subgroups, enhanced expression of genes coding for subunits of the Type A GABA receptor ($GABA_AR$), a chloride ion channel and major inhibitory neurotransmitter receptor. Using whole-cell patch clamp electrophysiology, we find that melanoma cells possess $GABA_ARs$ that control membrane permeability to anions. Select benzodiazepines, by enhancing $GABA_AR$ mediated anion transport, depolarize melanoma cell mitochondrial membrane potential and impair cell viability *in vitro*. Using a syngeneic melanoma mouse model, we find that a benzodiazepine promotes reduction in tumor volume when administered alone and potentiated radiation or immune checkpoint inhibitor α-PD-L1. When a benzodiazepine is combined with concurrent α-PD-L1 and a sub-lethal radiation dose, there is near complete loss of tumor, beyond what is observed for benzodiazepine with radiation or α-PD-L1. Mechanistically, benzodiazepine with radiation or α-PD-L1 results in ipsilateral and an abscopal tumor volume reduction commensurate with enhanced infiltration into the tumor milieu of polyfunctional CD8 T-cells. There is also an increased expression of genes with roles in the cytokine-cytokine receptor and p53 signaling pathways. This study provides evidence for melanoma cell $GABA_ARs$ as a therapeutic vulnerability with benzodiazepines promoting both direct and immune-mediated anti-tumor activity.

21. A PHASE II TRIAL OF COMPREHENSIVE TREATMENT BASED ON RADIOTHERAPY IN LEPTOMENINGEAL METASTASIS

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OBJECTIVES: To investigate the efficacy and security prospectively for patients with leptomeningeal metastases (LM) of comprehensive treatment based on radiotherapy. METHODS: From 2014 to 2017, 93 patients diagnosed with LM admitted to our hospital who underwent whole brain radiotherapy (WBRT) or craniospinal irradiation (CSI) with or without simultaneously boost were enrolled. The dynamic changes of enhanced magnetic resonance imaging, clinical signs and symptoms, cerebrospinal fluid cytology and liquid biopsy detection were recorded. The primary endpoint was overall survival (OS), the secondary endpoints were local control (LC), intracranial progress-free survival (IPFS), brain metastasis specific survival (BMSS) and toxicity. RESULTS: The major primary diagnosis was non-small cell lung cancer. Subjects received WBRT with boost (40 Gy in 20 fractions (f) for WBRT and 60Gy in 20 f for boost), focal radiation to LM, WBRT and CSI (40 Gy in 20 f or 50Gy in 25 f for WBRT and 36 Gy in 20 f for CSI). 20 patients were found tumor cells and were administrated intrathecal chemotherapy. 63 patients used target therapy. The median follow-up time was 33.8 months. OS/LC/IPFS at 1 year were 62.4%/77.2% and 52.6%, respectively. The median survival time was 15.9 months, and the median brain metastasis-specific survival was 42.2 months. Treatment-related grade 3–4 adverse events were rare and included eight grade 3 hematological toxicity. CONCLUSION: Reasonable comprehensive treatment including precise radiotherapy, intrathecal chemotherapy and targeted agents were well tolerated and could extend the survival time of LM patients compared with historical controls.

KEY WORDS: Leptomeningeal Metastasis; Tomotherapy; Comprehensive treatment

22. COMPARATIVE EFFICACY OF ALK-INHIBITORS IN ALK INHIBITOR-NAIVE ALK+ LUNG CANCER BRAIN METASTASES: A NETWORK META-ANALYSIS

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BACKGROUND: Lung cancer has been the leading cause of cancer death for both men and women worldwide. Non-small-cell lung cancer (NSCLC) displays an array of molecular abnormalities most commonly involving ALK and EGFR pathways. NSCLC with ALK rearrangements comprises around 5% of cases. Over the years, several ALK inhibitors (ALKI) have been approved with notable activity in brain metastases. However, there have been limited comparative studies exploring their relative efficacies. This analysis was conducted to compare the relative efficacy of ALKIs against ALKI-naïve ALK+ lung cancer brain metastases. METHODOLOGY: A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language; diagnosis of ALKI-naïve ALK+ lung cancer trials with brain metastases; treatment with Crizotinib (CRZ), Alectinib (ALC), Brigatinib (BRG), and Ceritinib (CER); and comparative studies reporting brain metastases specific responses/events. A Bayesian and a frequentists network meta-analysis were conducted using netmeta package and the random-effects model. RESULTS: Eight studies