In vivo anti-tumor activity of the PI3K inhibitor BKM120 – a MRI controlled therapy study

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Introduction

One of the current challenges in melanoma treatment to date is the high metastatic potential combined with the comparable low severity of symptoms that come along with the primary tumors. Brain metastases occur in 70% of patients with metastatic melanoma and are the leading cause of death in metastatic melanoma patients. Therefore it is of essential interest to develop suitable therapy strategies that effectively target cerebral metastases. Since the PI3K-akt signaling pathways play a major role in the progression and therapy resistance of brain metastases, independently of their mutation status therapy strategies that target this pathway are of essential interest. In this study a new PI3K inhibitor was investigated in a patient-derived BRAF-mutant brain metastasis melanoma cell line, injected into the brain of immunodeficient mice. To study the impact of the drug on the tumor growth longitudinally we used MRI to assess tumor volume. This longitudinal setup allows us to follow the tumor growth non-invasively and to analyze growth parameters rather then end point tumor size leading to an enormous increase of data quality and a massive reduction in animal numbers.

Materials and Methods

26 female CD-1 nude mice were injected intracranially with 1.5 x 10^6 WM3734 melanoma cells into the right hemisphere of the brain. Tumor growth was followed by a MRI treatment system twice a week using a MSME sequence on a 1 Tesla MRI system. Therapy started 20 days after tumor inoculation. 13 mice received a dose of 30mg/kg BKM120 per day orally, while the control group received sham treatment (Fig. 1). After two weeks of treatment, animals were sacrificed; brains were removed and prepared for histology.

Results

The comparison of the two MRI systems showed good concurrence by analyzing the growth pattern of the individual tumors in vivo without any treatment. Figure 3 shows the exponential growth pattern of an exemplary tumor measured with the 7 Tesla system using an anatomical TSE scan and the 1 Tesla system using a MSME sequence. The results demonstrated the capability of the 1T benchtop MRI system for anatomical brain tumor studies and was applied in the following therapy study. After intracranial injection, the tumor growth was followed weekly by a MRI treatment started at day 20 after tumor induction. Figure 4 shows the anatomical (1T MSME) images of two exemplary tumors under shamm (upper row) and inhibitor treatment (lower row).

Conclusion

Our data show that the new PI3K inhibitor had significant impact on the tumor growth of BRAF mutant WM3734 melanoma brain metastasis in vivo. Although it could not cause complete tumor remission in the restricted time frame of this study, tumor progression was significantly impared and tumor volumes even declined in single animals. Our imaging approach demonstrates the benefit of non-invasive in vivo tumor monitoring and shows the feasibility of these two methods in combination with our preclinical MRI scanner. Furthermore, longitudinal analysis approach fitting the exponential growth curves demonstrates the ability to reduce animal numbers while increasing the significance of the results enormously, from p = 0.0014 in the volume analysis and 5.4 x 10^{-10} in the growth slope analysis. To achieve the same p-value using the volume analysis we would need at least n = 34 animals per study group in this specific case. This analysis approach is only feasible on the basis of longitudinal in vivo imaging data.

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References:


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