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Marizomib activity as a single agent in malignant gliomas: Ability to cross the blood brain barrier.

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Abstract

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Background: Glioblastoma (GBM) is a highly aggressive brain tumor which displays innate resistance to multiple treatment modalities. Previous studies have shown that the proteasome plays a vital role in the physiology of GBM, and that proteasome inhibition can be used as a strategy for treating malignant gliomas. Marizomib is a second generation irreversible proteasome inhibitor which has a more lipophilic structure, suggestive of potential for penetration of the blood brain barrier (BBB), and has a broader and more prolonged inhibition proteasome inhibition profile than bortezomib and carfilzomib, the two proteasome inhibitors approved for treatment of multiple myeloma. While bortezomib and carfilzomib have little-no activity against malignant gliomas, marizomib could be a novel therapeutic strategy for primary brain tumors. Marizomib is presently in clinical trial for multiple myeloma. **Methods**: The *in vitro* antitumor activity of marizomib was studied in human glioma lines U251 and D54. The ability of marizomib to cross the BBB and regulate proteasome activities was evaluated in cynomolgus monkeys and rats. The anti-tumor effect of marizomib *in vivo* was tested in an orthotopic xenograft model of human GBM. **Results**: Marizomib inhibited survival of U251 and D54 by ~90% at 60nM and markedly decreased GBM cell migration and invasion. While marizomib induced increased free radical production and apoptosis, the reactive oxygen species quenching agent NAC blocked these effects. In rats, marizomib distributed into the brain at 30% of blood levels, and the monkey studies revealed robust baseline chymotrypsin-like (CT-L) proteasome activity in brain tissue that was significantly inhibited (> 30%) in animals treated with marizomib. Similar effects were seen against the caspase-like activity. Encouragingly, mice treated with marizomib survived significantly longer than the control animals ($p < 0.05$). **Conclusions**: These preclinical studies demonstrate that marizomib can cross the BBB and inhibit proteasome activity in primate brain, and elicit a significant anti-tumor effect in a rodent intracranial model of malignant gliomas. Marizomib is in Phase 1 clinical testing for malignant gliomas.