A phase II trial evaluating the effects and intra-tumoral penetration of bortezomib in patients with recurrent malignant gliomas.


Abstract

One resistance mechanism in malignant gliomas (MG) involves nuclear factor-κB (NF-κB) activation. Bortezomib prevents proteasomal degradation of NF-κB inhibitor α (NFKBIA), an endogenous regulator of NF-κB signaling, thereby limiting the effects of NF-κB on tumor survival and resistance. A presurgical phase II trial of bortezomib in recurrent MG was performed to determine drug concentration in tumor tissue and effects on NFKBIA. Patients were enrolled after signing an IRB approved informed consent. Treatment was bortezomib 1.7 mg/m² IV on days 1, 4 and 8 and then surgery on day 8 or 9. Post-operatively, treatment was Temozolomide (TMZ) 75 mg/m² PO on days 1-7 and 14-21 and bortezomib 1.7 mg/m² on days 7 and 21 [1 cycle was (1) month]. Ten patients were enrolled (8 M and 2 F) with 9 having surgery. Median age and KPS were 50 (42-64) and 90 % (70-100). The median cycles post-operatively was 2 (0-4). The trial was stopped as no patient had a PFS-6. All patients are deceased. Paired plasma and tumor bortezomib concentration measurements revealed higher drug concentrations in tumor than in plasma; NFKBIA protein levels were similar in drug-treated vs. drug-naïve tumor specimens. Nuclear 20S was less in the cytoplasm in postoperative samples. Postoperative treatment with TMZ and bortezomib did not show clinical activity. Bortezomib appears to sequester in tumor but pharmacological effects on NFKBIA were not seen, possibly obscured due to downregulation of NFKBIA during tumor progression. Changes in nuclear 20S could be marker of bortezomib effect on tumor.

KEYWORDS: Bortezomib; Malignant glioma; Nuclear factor-κB; Temozolomide

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