Preclinical Experimental Therapeutics

**Polynuclear platinum anticancer drugs are more potent than cisplatin and induce cell cycle arrest in glioma**

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We have evaluated the efficacy of the multinuclear platinum chemotherapeutics BBR3464, BBR3571, and BBR3610 against glioma cells in culture and animal models and investigated their mechanism of action at the cellular level. In a clonogenic assay, BBR3610, the most potent compound, had an IC₉₀ dose (achieving 90% colony formation inhibition) that was 250 times lower than that of cisplatin for both LNZ308 and LN443 glioma cells. In subcutaneous xenografts of U87MG glioma cells, BBR3610 approximately doubled the time it took for a tumor to reach a predetermined size and significantly extended survival when these cells were implanted intracranially. Analysis of apoptosis and cell cycle distribution showed that BBR compounds induced G2/M arrest in the absence of cell death, while cisplatin predominantly induced apoptosis. Interestingly, the BBR compounds and cisplatin both induced extracellular signal-regulated kinase 1/2 phosphorylation, and inhibition of this pathway at the level of MEK antagonized the induction of G2/M arrest or apoptosis, respectively. Analysis of Chk1 and Chk2 status did not show any differential effects of the drugs, and it is thus unlikely to underlie the difference in response. Similarly, the drugs did not differentially modulate survivin levels, and knockdown of survivin did not convert the response to BBR3610 to apoptosis. Together, these findings support continued development of BBR3610 for clinical use against glioma and provide a framework for future investigation of mechanism of action.

**Key Words:** glioma • multinuclear platinum • chemotherapy • ERK • extracellular signal-regulated kinase • G2/M arrest

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