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Neural stem/progenitors and glioma stem-like cells have differential sensitivity to chemotherapy.

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Abstract

OBJECTIVES: New data suggest that glioma stem-like cells (GSCs) and neural stem/progenitor cells (NSCs) may share common origins. GSCs drive tumor proliferation and appear to be resistant to classic chemotherapy, while the effects of chemotherapy on NSCs are not well studied. As the role of NSCs in learning and memory is increasingly recognized, we need to identify drugs that reduce neurotoxicity but are still effective against glial tumors.

METHODS: We treated 3 human NSC cultures and multiple low- and high-grade GSC cultures with the commonly used agents temozolomide (TMZ) and cisplatin (CIS), and with 2 newer, promising drugs: the proteasome inhibitor bortezomib (BTZ) and the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (ERL). We measured cell survival, proliferation, cell death induction, and drug resistance markers.

RESULTS: TMZ decreased NSC viability, while minimally affecting GSCs. TMZ induced NSC death, which was partially compensated for by increased proliferation. CIS had similar effects. The NSC's sensitivity to TMZ and CIS correlated with low expression of the multidrug resistance gene ABCG2, but not of MGMT or MSH1/MLH2. BTZ caused an 80% decrease in GSCs, while minimally affecting NSCs. GSCs had lower proteasome levels and activity after BTZ treatment. ERL treatment also decreased GSC numbers, but not NSC viability, which correlated with low EGFR expression in NSCs compared to GSCs.

CONCLUSIONS: Newer chemotherapy agents ERL and BTZ are effective against GSCs yet produce minimal effects on NSCs, while the older drugs TMZ and CIS are more toxic for NSCs than for GSCs. The identification and testing of more selective drugs is clearly warranted.

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