

Primary malignancies of the CNS and metastasis that found sanctuary in the brain have invariably a poor prognosis. Although certain antineoplastic agents are known to be active against such tumors, their entry into the brain is restricted. This is for an important part due to the presence of the blood-brain barrier, as well as the high P-gp content of the endothelial cells of the CNS circulation, making chemotherapy of these tumors often unsuccessful. Recently, we observed that a regimen alternating BCNU with VP-16 and high-dose, oral Tmx induced partial responses in patients with inoperable glioblastoma, who progressed after surgery and brain irradiation. BCNU, VP-16, as well as Tmx have activity in brain tumors. Considering that VP-16 and Tmx may share common cellular targets - P-gp and tyrosine kinase - a potential synergism of this regimen can be suggested. We tested this hypothesis in a rat model, where the animals were treated with either VP-16 alone, Tmx alone, or VP-16 plus Tmx. VP-16 and Tmx were given at the dose of 100 and 180 mg/m², respectively, for a 5-days period. A difference in the CNS disposition of VP-16 and Tmx with each of the regimens was assessed using HPLC, after homogenization, delipidization and chloroform/methanol extraction. The data from this study can provide support for the design of regimens with improved efficacy in brain malignancies.