Clinical Therapy Trials—Radiation

Phase 2 trial of radiation plus high-dose tamoxifen for glioblastoma multiforme: RTOG protocol BR-0021¹


University of Wisconsin, Madison, WI 53792 (H.I.R., M.P.M.); Radiation Therapy Oncology Group, Philadelphia, PA 19106 (M.W., W.F.S.); Medical College of Wisconsin, Milwaukee, WI 53224 (C.J.S.); LDS Hospital, Salt Lake City, UT 84143 (A.K.C.); Foundation for Cancer Research and Education, Phoenix, AZ 85013 (D.G.B.); and Summa Health Systems, Akron, OH 44309 (W.F.D.); USA

² Address correspondence to H. Ian Robins, Comprehensive Cancer Center, CSC K4/534, University of Wisconsin, 600 Highland Avenue, Madison, WI 53792-6164 (hirobins@wisc.edu).

Preclinical studies support the concept that inhibition of protein kinase C (PKC) by tamoxifen (TAM) should provide both antineoplastic effects and radiosensitization. High-dose TAM (80 mg/m² p.o. daily in divided doses) was given with and after conventional radiotherapy (XRT) to inhibit PKC-mediated signaling, which is known to be enhanced in glioblastoma (GBM). Seventy-seven patients were accrued between December 2000 and December 2001; two were ineligible and not included in the efficacy results. Pretreatment characteristics of the patients included the following: 52% were less than 60 years of age, 39% had a Zubrod score of 0, 70% had minor or no neurological symptoms, and 65% were Radiation Therapy Oncology Group-recursive partition analysis (RPA) class III and IV. Eighty-six percent of patients achieved acceptable dosing of TAM. Notable toxicity included late radiation grade 3 in two patients and thromboembolic events in 16 patients (two grade 2, 10 grade 3, three grade 4, and one grade 5), for an incidence of 20.8% (which is lower than expected, based on the literature for deep vein thrombophlebitis in GBM patients not receiving TAM). Median survival time (MST) was 9.7 months as compared (by three different statistical methodologies) to the historical GBM control database of 1457 RPA class III, IV, and V drug/XRT-treated patients. After controlling for RPA class IV, the MST was 11.3 months, which compares to the historical RPA control of 11.3 months ($P = 0.37$). The results obtained do not exhibit a substantial advance over those of previous studies with various XRT/drug doublets, including BCNU. However, as TAM does not have significant overlapping toxicities with most other drugs, its testing in a combined modality approach with other medications may be justified in future clinical trials. Historically, the incidence of thromboembolic events in GBM patients is approximately 30%. The lower-than-expected incidence seen here has also been observed in other high-dose TAM GBM studies. We speculate that TAM inhibited the PKC-mediated phosphorylation of coagulation factors.

**Key Words:** glioblastoma multiforme • radiation • tamoxifen

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