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Rationally designed pharmacogenomic treatment using concurrent capecitabine and radiotherapy for glioblastoma; gene expression profiles associated with outcome.

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Abstract

PURPOSE: Previous preclinical studies suggested that concurrent capecitabine and radiation could be an effective new treatment modality for glioblastoma (GBM). In the current study, we investigate toxicity and response to this regimen and explore associations between gene expression and patient outcome. **EXPERIMENTAL DESIGN:** Eighteen newly diagnosed GBM patients received concurrent capecitabine at 625 mg/m² BID (25% escalation) and irradiation (60 Gy total) for 6 weeks followed by 4 weeks of capecitabine only. Maintenance capecitabine was administered for 14 days every 3 weeks until progression or unacceptable toxicity. Expression analysis of 94 genes involved in capecitabine metabolism and radiation response was done on tissues obtained before therapy. The relationship of gene expression with time-to-progression (TTP) and overall survival (OS) was investigated using univariate Cox proportional hazards regression, semi-supervised principle component analysis, and class prediction modeling. **RESULTS:** The maximum tolerated dose of capecitabine was 625 mg/m² BID. Median patient TTP and OS were 247 and 367 days, respectively. Cox regression identified 24 genes significantly ($P < 0.025$) associated with patient outcome. Semi-supervised principle component analysis identified two patient populations significantly different in both TTP ($P = 0.005$) and OS ($P = 0.015$). Class prediction modeling determined that eight genes (RAD54B, MTOR, DCTD, APEX2, TK1, RRM2, SLC29A1, and ERCC6) could collectively classify patients into outcome subgroups with 100% accuracy and precision. **CONCLUSIONS:** Capecitabine and concurrent radiation for newly diagnosed GBM seems to be well tolerated and comparable to temozolomide and radiation. A gene expression profile predictive of patient outcome that may be useful in patient stratification for therapy was also elucidated. Copyright (c) 2010 AACR.

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