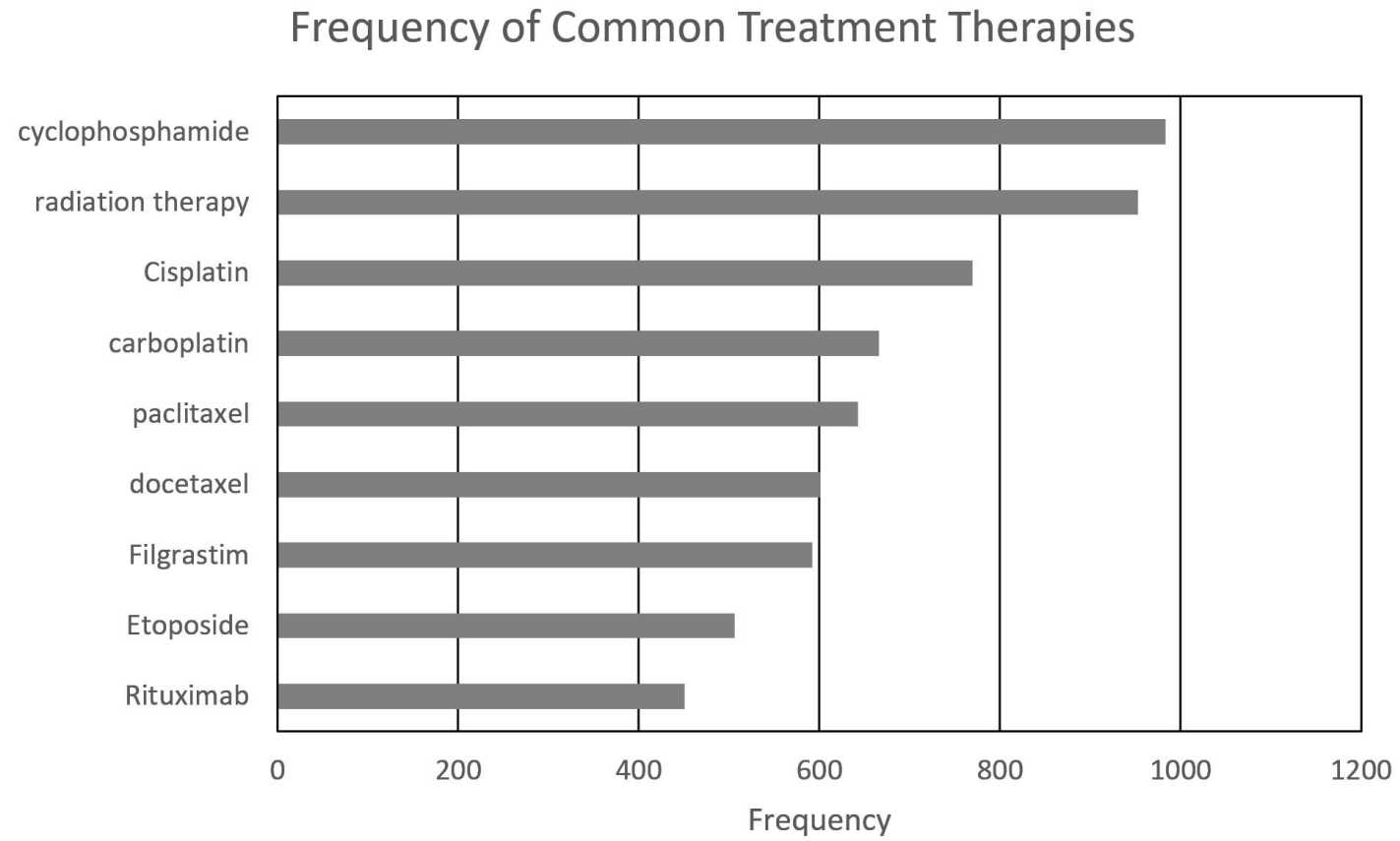
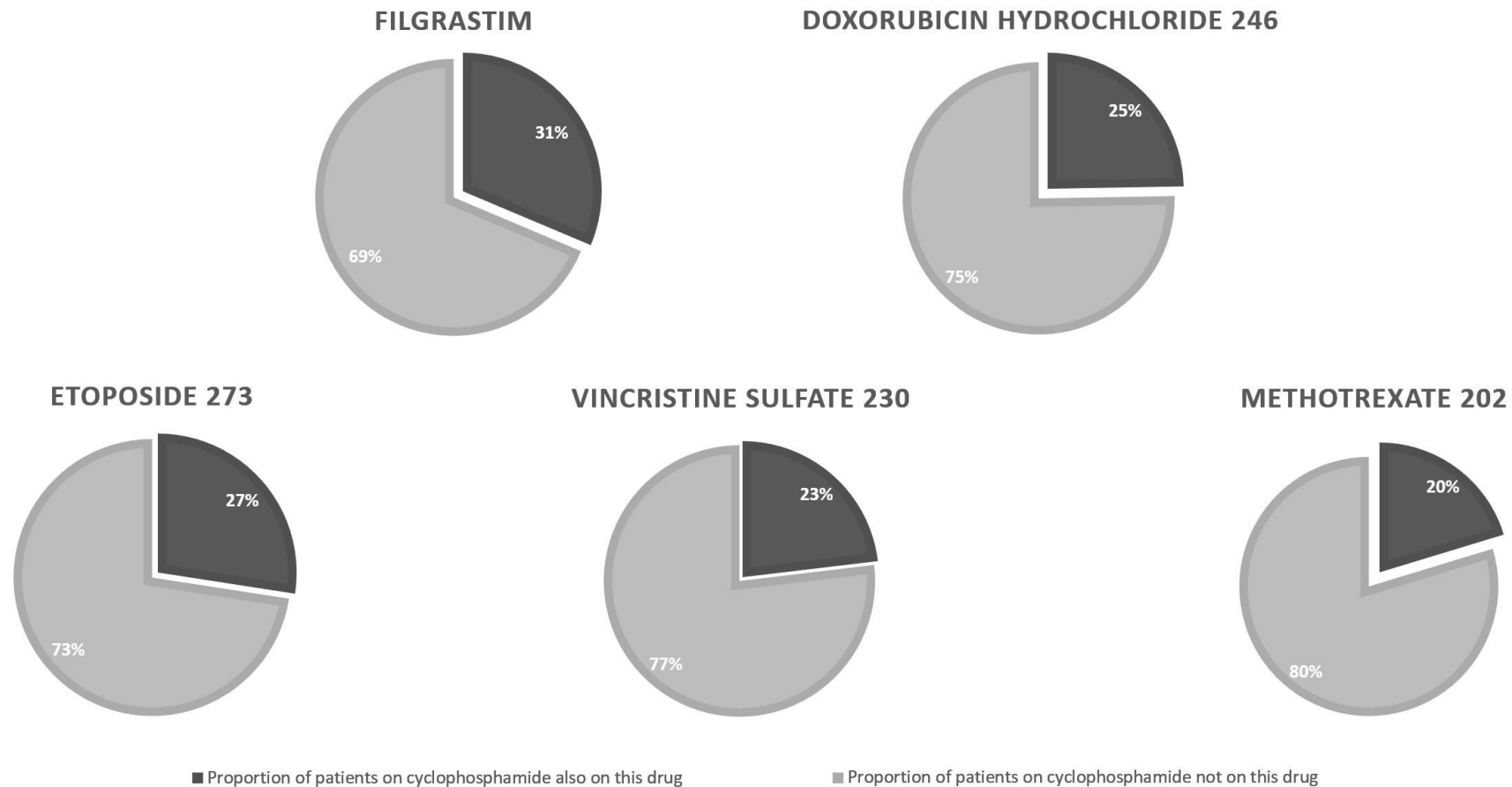


Interventions from Clinical Trial Reports

Landscape of Interventions



Combinations involving cyclophosphamide



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Design of a Neoadjuvant Glioblastoma Trial with Short-Term, Tissue-Based Endpoints

Our primary motive in conducting this single-arm study was to follow up on the compelling preclinical activity of mTOR inhibitors in PTEN-null cancer models by designing a small clinical trial focused on measuring antitumor activity using short-term endpoints. To enhance the probability of success based on the preclinical hypothesis, we restricted enrollment to those patients with recurrent glioblastoma whose tumors had evidence of PTEN loss based on an analysis of tissue obtained from the initial resection (S1) (Figure 1). Eligibility was also limited to those patients scheduled to undergo salvage surgical resection (S2) so that tumor tissue would be available for assessing the endpoints of mTOR inhibition and tumor cell proliferation, as well as intratumoral rapamycin concentrations. By mandating access to pre- and posttreatment samples for each patient, this trial design allows inpatient comparison of molecular endpoints, thereby enhancing the statistical power to detect changes in a small sample size. To provide confidence that any S1-to-S2 changes could be attributed to rapamycin treatment, we conducted an identical set of measurements using S1 and S2 samples from nine glioblastoma patients who did not receive rapamycin (controls).

Enrollment in the Phase I clinical trial was restricted to patients whose initial tumor resection ("surgery 1") specimen was PTEN-deficient by immunohistochemistry. Patients were enrolled after failing standard therapy with radiation and chemotherapy (i.e., "tumor recurrence"). Prior to the scheduled salvage tumor resection ("surgery 2"), patients received a short course (mean: 7.5 d) of oral rapamycin. Rapamycin was resumed after recovery from surgery until patients developed clinical and/or radiographic evidence of treatment failure. The effects of rapamycin on tumor cell proliferation and mTOR signaling in tumor tissue were determined by comparing the tumor tissue collected during salvage resection ("surgery 2") with a sample of the same tumor collected during the initial tumor resection ("surgery 1"). Time-to-progression (TTP) was defined as the interval between start of rapamycin therapy and postoperative treatment failure.

Patients whose tumors had PTEN loss were identified using a previously reported semi-quantitative scoring system that evaluates PTEN expression in tumor cells relative to adjacent vascular endothelial cells [17,18]. We screened tumor samples obtained at the time of initial surgery (S1) from 165 glioblastoma patients followed at our institution for subsequent neuro-oncology care. Either complete (43/165) or partial (24/165) loss of PTEN immunoreactivity was shown in 67/165 (40.6 %) of tumors. Fifteen patients with PTEN-deficient tumors, who also met all other eligibility criteria (see Methods, Texts S2 and S3), were enrolled at the time of tumor recurrence and received neoadjuvant oral daily rapamycin (2 mg, 5 mg, or 10 mg per day) for approximately 1 wk (median: 6 d, mean: 7.5 d) (Table 1) prior to salvage surgical resection (S2). Matching S1 and S2 samples were used to evaluate the effects of rapamycin on tumor cell proliferation and mTOR activity. After recovery from surgery, patients resumed daily rapamycin treatment at the neoadjuvant dose until clinical and/or radiographic evidence for tumor progression was found.

Clinical Characteristics of Rapamycin Study Patients

Paper Title:

Antitumor Activity of Rapamycin in a Phase I Trial for Patients with Recurrent PTEN-Deficient Glioblastoma

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