Inability of positive phase II clinical trials of investigational treatments to subsequently predict positive phase III clinical trials in glioblastoma.


BACKGROUND: Glioblastoma is the most common primary malignant brain tumor in adults, but effective therapies are lacking. With the scarcity of positive phase III trials, which are increasing in cost, we examined the ability of positive phase II trials to predict statistically significant improvement in clinical outcomes of phase III trials.

METHODS: A PubMed search was conducted to identify phase III clinical trials performed in the past 25 years for patients with newly diagnosed or recurrent glioblastoma. Trials were excluded if they did not examine an investigational chemotherapy or agent, if they were stopped early owing to toxicity, if they lacked prior phase II studies, or if a prior phase II study was negative.

RESULTS: Seven phase III clinical trials in newly diagnosed glioblastoma and 4 phase III clinical trials in recurrent glioblastoma met the inclusion criteria. Only 1 (9%) phase III study documented an improvement in overall survival and changed the standard of care.

CONCLUSION: The high failure rate of phase III trials demonstrates the urgent need to increase the reliability of phase II trials of treatments for glioblastoma. Strategies such as the use of adaptive trial designs, Bayesian statistics, biomarkers, volumetric imaging, and mathematical modeling warrant testing. Additionally, it is critical to increase our expectations of phase II trials so that positive findings increase the probability that a phase III trial will be successful.

KEYWORDS: clinical trials; glioblastoma; phase II; phase III

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