ABSTRACT

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Poor correlation between preclinical and patient efficacy data for tumor targeted monotherapies in glioblastoma: the results of a systematic review.

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PURPOSE: Limited progress has been made in treating glioblastoma, and we hypothesise that poor concordance between preclinical and clinical efficacy in this disease is a major barrier to drug development. We undertook a systematic review to quantify this issue.

METHODS: We identified phase I trials (P1Ts) of tumor targeted drugs, subsequent trial results and preceding relevant preclinical data published in adult glioblastoma patients between 2006-2019 via structured searches of EMBASE/MEDLINE/PUBMED. Detailed clinical/preclinical information was extracted. Associations between preclinical and clinical efficacy metrics were determined using appropriate non-parametric statistical tests.

RESULTS: A total of 28 eligible P1Ts were identified, with median ORR of 2.9% (range 0.0-33.3%). Twenty-three (82%) had published relevant preclinical data available. Five (18%) had relevant later phase clinical trial data available. There was overall poor correlation between preclinical and clinical efficacy metrics on univariate testing. However, drugs that had undergone in vivo testing had significantly longer median overall survival (7.9 vs 5.6mo, p = 0.02). Additionally, drugs tested in ≥ 2 biologically-distinct in vivo models ('multiple models') had a significantly better median response rate than those tested using only one ('single model') or those lacking in vivo data (6.8% vs 1.2% vs. 0.0% respectively, p = 0.027).

CONCLUSION: Currently used preclinical models poorly predict subsequent activity in P1Ts, and generally over-estimate the anti-tumor activity of these drugs. This underscores the need for better preclinical models to aid the development of novel anti-glioblastoma drugs. Until these become widely available and used, the use of multiple biologically-distinct in vivo models should be strongly encouraged.

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