INPLASY PROTOCOL

To cite: Gupta et al. Meta-Analysis of Standard Temozolomide versus Extended Adjuvant Temozolomide following concurrent Radiochemotherapy in newly-diagnosed Glioblastoma (MASTER-G). Inplasy protocol 2021120114. doi: 10.37766/inplasy2021.12.0114

Received: 24 December 2021

Published: 24 December 2021

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Support: **None.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None declared.

Meta-Analysis of Standard Temozolomide versus Extended Adjuvant Temozolomide following concurrent Radiochemotherapy in newly-diagnosed Glioblastoma (MASTER-G)

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Review question / Objective: **To assess the safety and efficacy of extended adjuvant temozolomide compared to standard adjuvant temozolomide after concurrent radiochemotherapy in patients with newly-diagnosed glioblastoma.**
Condition being studied: **Newly-diagnosed glioblastoma.**
Eligibility criteria: **Prospective clinical trials randomly assigning patients to extended (>6-cycles) adjuvant TMZ (experimental arm) or standard (6-cycles) adjuvant TMZ will be included. Randomization in an individual study may have been done upfront before concurrent phase (RT/TMZ), after completion of concurrent RT/TMZ and before starting adjuvant phase, or after completion of standard adjuvant TMZ (6-cycles). Emulated RCTs, quasi-randomized trials, propensity matched analyses, non-randomized comparative studies, or observational studies will not be considered in this review.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 December 2021 and was last updated on 10 March 2023 (registration number INPLASY2021120114).

INTRODUCTION

Review question / Objective: **To assess the safety and efficacy of extended adjuvant temozolomide compared to standard adjuvant temozolomide after concurrent radiochemotherapy in patients with newly-diagnosed glioblastoma.**

Rationale: **Retrospective analysis provides conflicting and contradictory results in this regard with some studies suggesting potential benefit while others reporting lack of survival benefit but risk of increased hematologic toxicity. Hence a critical apprisal of all available evidence with pooling of data from randomized controlled**

trials is required to generate high-quality evidence.

Condition being studied: Newly-diagnosed glioblastoma.

METHODS

Search strategy: An electronic search of Medline via PubMed will be conducted with no language, year, or publication status restrictions. Different key-words including Medical Subject Heading (MeSH) terms such as "Glioblastoma"[MeSH] OR “GBM” AND "Temozolomide"[MeSH]) OR “TMZ” [MeSH] AND “extended adjuvant[MeSH]” OR "prolonged adjuvant” will be combined using Boolean operations. The Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effectiveness (DARE) will also be searched electronically. Electronic search will be further supplemented by hand-searching of review articles, cross references and conference proceedings.

Participant or population: Newly-diagnosed glioblastoma.

Intervention: Extended adjuvant temozolomide (>6-cycles of TMZ).

Comparator: Standard adjuvant temozolomide (6-cycles TMZ).

Study designs to be included: Randomized controlled trials (RCTs) plus emulated RCTs, quasi-randomized trials, propensity matched analyses, and non-randomized comparative studies will be considered for inclusion in the systematic review and meta-analysis.

Eligibility criteria: In addition to RCTs, emulated RCTs, quasi-randomized studies, propensity matched analyses, and non-randomized comparative studies will be eligible for inclusion in the systematic review and meta-analysis. Comparative studies with non-extractable data will be excluded from evidence-synthesis.

Information sources: PubMed, CENTRAL, DARE databases.

Main outcome(s): Measures of efficacy will include survival outcomes; primary outcome of interest will be overall survival (OS) while progression-free survival (PFS) will be considered as secondary outcome measure. OS will be defined as the time interval between date of diagnosis (surgery) and last contact or death from any cause. PFS will be calculated from diagnosis till documented clinico-radiological progression, last contact, or death whichever occurs earlier. Safety outcomes will include comparison of TMZ-induced grade 3 or worse hematologic toxicity (anemia, neutropenia, and thrombocytopenia) during adjuvant TMZ.

Additional outcome(s): None.

Data management: All extracted data will be vested with the Principal Investigator.

Quality assessment / Risk of bias analysis: Quality assessment of non-RCTs will be done using the modified Newcastle-Ottawa scale for non-randomized comparative studies.

Strategy of data synthesis: Two reviewers will independently read each abstract, pre-print, publication, protocol, or any other available study report and extract relevant data from individual primary studies using a study-specific data extraction form. Discrepancy, if any, will be resolved through consensus interpretation by a third reviewer. Extracted data will include but not be necessarily limited to study characteristics, patient characteristics, number of participants randomised per arm, intervention details, and outcomes. Survival outcomes for individual patients will be extracted manually from the published Kaplan-Meier survival curves using WebPlot digitizer. Using this individual participant level extracted data and published numbers at risk, survival curves for OS and PFS for each study will be reconstructed. The number of events and the time points (t-risk and n-risk) will be extracted from published data. If not reported explicitly, the same will be derived from available graphs as precisely as possible to generate composite Kaplan-

Meier survival curves that includes individual-level data from all four RCTs. The hazard ratio (HR) with corresponding 95% confidence interval (CI) will be computed for each individual primary study and also compared with the published HR (95%CI) if reported and reconciled prior to statistical pooling. Grade 3 or worse hematologic toxicity (anemia, neutropenia, and thrombocytopenia) will be compared between the two arms and will be reported as risk ratio (RR) with 95%CI. All data will be pooled using the random-effects model and will be expressed as HR or RR as appropriate with corresponding 95%CI. Any p-value <0.05 will be considered as statistically significant.

Subgroup analysis: Subgroup analysis will be done based on MGMT methylation status.

Sensitivity analysis: Sensitivity analysis will be done for overall survival by dropping individual study at one time and recalculating the outcomes to see whether one single study was influencing the results.

Language: English.

Country(ies) involved: India.

Other relevant information: None.

Keywords: glioblastoma; temozolomide; extended; adjuvant; survival; toxicity.

Dissemination plans: Results will be presented in national/international meetings and will also be submitted for publication in indexed peer-reviewed journals

Contributions of each author:

Author 1 - Tejpal Gupta - Study concept and design, literature search, statistical analysis, and final draft of manuscript.
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Author 2 - Riddhijyoti Talukdar - Extraction of data including digitization of curves independently and writing first draft of manuscript.
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