Pooled Efficacy Analysis of Phase II Clinical Trials of Recurrent Glioblastoma

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

School of Pharmacy
Brac University
October 2024

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Pooled Efficay Analysis of Phase II Clinical Trials of Recurrent Glioblastoma" submitted by Farzana Islam (20346004), of Spring, 2024 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trials.

Abstract

Recurrent glioblastoma require more research due to its wide spread prevalence among people. Researchers are working tirelessly to enhance the accessibility, ease the evaluation as well as ensure the validation of the end points in clinical trials. In this study, we analyzed 391 Phase II clinical trials endpoints [236 Progression Free Survival (PFS), 225 Overall Survival (OS), 214 Overall Response Rate (ORR) and 37 Duration of Response (DOR)] in order to examine the efficacy and impact of anti-cancer agent in recurrent glioblastoma. We assessed the treatment effects for OS, PFS, ORR and DOR by using appropriate statistical methods. We observe statistically significant moderate positive correlation between PFS and OS (r = 0.48, 95% CI = 0.37-0.57, p < 0.00001). Similarly, there is a statistically significant weak positive correlation between ORR and OS (r = 0.14, 95% CI = 0.0012-0.28, p = 0.047). In contrast, there is no significant correlation between DOR and OS (r = 0.19, 95% CI = -0.161-0.502, p = 0.283). Moreover, linear regression analysis performed on full model (adjusted R^2 = 0.2) showed that the independent variables (mPFS, ORR, wECOG, Age, Treatment Size and Targeted Agent) predicted the OS with 20% accuracy. However, in reduced model the independent variables (mPFS, ORR, Treatment Size & Targeted Agent) predicted the OS with 13% accuracy. Furthermore, mean PFS and mean OS of chemotherapy are greater than targeted therapy but p value in both the cases came higher than 0.05 which means obtained result is not statistically significant. On the other hand, mean ORR of targeted therapy is greater in comparison to chemotherapy but the p value (0.176) shows the obtained result is not statistically significant. Therefore, further studies with a larger datasets are required to validate our findings.

Key words: Recurrent glioblastoma, phase II clinical trial, efficacy endpoints, progression free survival, overall survival, overall response rate, duration of response, linear modeling.

Dedication

I want to dedicate this to my parents for being constant source of strength throughout my journey.

Acknowledgement

I would like to express my deepest gratitude to Almighty Allah for blessing with strength, guidance and perseverance throughout my journey. Then I want to extend my heartfelt gratitude to my parents and siblings for showing immense love and supporting me in every single step to overcome all the obstacles.

I would like to thank specially my supervisor Faruque Azam, Lecturer of School of Pharmacy, Brac University for his unwavering support, valuable guidance and encouragement throughout my project work which allowed me to shape my work beautifully. It would not be possible for me to complete this project without her insightful advice. My heartfelt gratitude also goes out to all the faculty members of School of Pharmacy, Brac University for believing in me and guiding me throughout my academic journey.

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List of Acronyms:

GBM	Glioblastoma
PFS	Progression Free Survival
TTP	Time to Progression
OS	Overall Survival
ORR	Overall Response Rate
DOR	Duration of Response
wECOG	Weighted Eastern Cooperative Oncology Group
BME	Brain Microenvironment
ISS	Interstitial System
CNS	Central Nervous System
TMZ	Temozolomide

Chapter 1

Introduction

1.1 The Brain and Brain Diseases

The human brain is the control center for the nervous system. It helps in the formation of memory, thoughts, emotions and movement by a complicated function which is called the top most product of biological evolution. The most important goal of a person's life is to be able to maintain a healthy brain in order to maintain good health and longevity (Wang et al., 2020). The brain consumes the highest amount of energy in the body. In order to satisfy the energy demand of the brain, it requires processes like: compartmentalized, cell-specific metabolic processes and all these processes are known as complementary as well as intimately coupled. Thus, the brain fully depends on orchestrated energy-obtaining agents, processes as well as molecular features including the neurovascular unit, the astrocyte–neuron metabolic coupling and the cellular distribution of energy substrate transporters (Ardanaz et al., 2022). Brain tissues are made up of three compartments including the interstitial system (ISS), neural cells and vascular system. Neural cells known as the most significant functional element of the brain occupy only 70% to 80% of the entire volume of the brain. The brain microenvironment (BME) formed by ISS along with the vascular system. The rest of the volume of the brain is occupied by the brain microenvironment and it ultimately provides the living environment for neural cells. Almost 5% to 20% of the total brain volume is occupied by ISS. Traditionally it was considered as a gap filler play a vital role only in the cell maintenance and adherence. However, most recent studies have shown that the brain ISS plays numerous vital roles in brain function. For instance: processing information as well as interrogating the processed information, maintaining communication among neural cells and giving coordinating response, if any change detected in the internal and external environment of the brain (Lei et al., 2017). The brain is made up two different cells including neurons and glial cells where the neuron sends and receives nerve impulses. In contrast, the glial cells play significant role in nervous system by developing myelin, maintain homeostasis, improving the signal transmission process. In the human brain, the number of neurons are 50 times less than that of glial cells.

If any dysfunction, disease or deformities are seen in the brain, the entire body gets affected. The brain is prone to neuron or tissue infection and neuronal disease. Generally, human brain disorders are categorized into two types such as: Neuropsychiatric disorders and Neurodegenerative diseases. Basically, neuropsychiatric disorders are a type of disorder which deals with mental disruption that occurs because of the improper functioning of the brain. On the other hand, neurodegenerative diseases are a composite form of disorders that is represented by progressive loss of neurons. Activity of both the central nervous system (CNS) and peripheral nervous system (PNS) are hindered by neurodegenerative diseases (Naz & Siddique, 2020). Brain diseases include brain infections like: meningitis, encephalitis and brain abscess. It also include brain trauma like concussion and intra-cerebral hemorrhage as well as stroke. Brain disorders result in memory problems, vision problems, convulsions and muscle impairment. Meningitis of the brain tissues, spinal cord inflammation and lining around the brain are the root causes of all the brain diseases are. Brain abscess is basically a mass of pus developed in the brain tissue due to fungal or bacterial infection. People with compromised immune systems are prone to suffer from brain abscess. Brain tumor is the most dangerous disease and it has prevalence among human beings (Erasa & Meena, 2017).

1.2 Brain Tumor and Types

Brain tumors are abnormal tissue mass mainly originate in the brain. Brain is involved as metastatic site for all the tumors. The 2007 classification of CNS tumors (grade I to grade IV) has been acknowledged by the World Health Organization (WHO). This classification categorized tumors into four different types or degrees of malignancy. Gliomas are the collection of 80% of the primary malignant tumor that is originating from glial cells. There are 4 different types of gliomas including (1) Astrocytoma (tumors obtained from astrocytes). They are graded I to IV. Here, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, glioblastoma multiforme are known as grade I, II, III and IV respectively. (2) oligodendrogliasare made up of oligodendrocytes. All around the neurons a protective coating is formed by the oligodendrocytes cells. They are normally classified as grade II (oligodendroglioma) and III (anaplastic oligodendroglioma) and (3) ependymomas, the last type of gliomas, originated from ependymal cells, involved in lining the ventricles, the brain fluid-filled cavities and the central canal of the spinal cord. They are categorized as grade I, II and III that are called myxopapillar ependymomas, ependymomas and anaplastic ependymomas respectively (Malhotra et al., 2015).

1.3 Glioblastoma

1.3.1 Definition

The glioblastoma multiforme (GBM) is the most aggressive and common primary malignant brain tumor among the various grades and types of gliomas (McFaline-Figueroa & Lee, 2018). Glioblastoma is not only aggressive but also unavoidably recurrent which is mainly seen in the primary intra-axial brain tumor along with a dismal prognosis (Oronsky et al., 2021). This most prevalent malignant brain tumor is the root cause of more than 50% of all primary malignant tumor observed in CNS. It originates in the glial cells. Glioblastoma mainly surround and support nerve cells in the brain that are commonly found in the four lobes of brain. It mainly seen in frontal lobe, followed by the temporal, parietal, and occipital lobes. It is categorized as grade IV tumor in order to indicate its high degree of malignancy. These tumors are highly invasive and spread extensively in the brain tissue. As a result, it becomes difficult to remove these tumors surgically and they often remain incomplete. 70% of newly diagnosed cases of this dangerous primary tumor of the CNS that is mainly seen in people older than 65 years old and the age-adjusted incidence rate is 3.22 per 100,000 (Chen et al., 2021).

1.3.2 Sub-types of Glioblastoma

Glioblastoma (GBM) is classified into 4 subtypes based on its genomic features: Proneural (PN), Neural (NE), Classical (CL) and Mesenchymal (ME) (Mao et al., 2022). The proneural subtype is characterized by gene expression of platelet-derived growth factor receptor alpha as well as frequent isocitrate dehydrogenase 1 (IDH1) mutation. It is found mainly in younger patients. The proneural subtypes probably have a better survival rate than other three subtypes of glioblastoma. In the tumor microenvironment non-tumor cells are found that are also known as neural glioblastoma. On the other hand, the mesenchymal subtype of glioblastoma tend to show increased expression of markers of angiogenesis. It include various types of genes like: vascular endothelial growth factor gene, vascular endothelial growth factor receptor 1 gene, vascular endothelial growth factor receptor 2 gene as well as endothelial marker platelet endothelial cell adhesion molecule gene and all these genes show mesenchymal and angiogenic features (Zhang et al., 2020). In the classical subtype, 97% of gliomas exhibit highest levels of the Epidermal Growth Factor Receptor (EGFR) amplification where in over one-third of cases have shown EGFR mutation (R. Chen et al., 2017).

1.3.3 Conventional Treatment Options for Glioblastoma

Traditionally, glioblastoma and its subtypes were treated by surgery, radiotherapy and chemotherapy. All these methods are routinely used in clinics. In the early 1980s, scientists began to remove brain tumors surgically and the aim was to remove the maximum number of tumor in order to get better outcome and to get brain tissue. Brain tissue is utilized to perform pathological analysis (Yalamarty et al., 2023). Regrettably, the depth of surgical resection of brain tumors are inevitably constrained by the cerebral anatomy so that impairing the neurological function can be avoided (Putavet & De Keizer, 2021). In addition, post-surgery cytotoxic as well as anti-angiogenic chemotherapy agents are used to treat GBM. This standard therapy includes 6 weeks of concurrent temozolomide (TMZ) and radiation therapy, followed by adjuvant temozolomide (TMZ). The drug also has radiation-sensitizing properties that result in enhanced radiation-induced cancer cell death when used in combination with radiation therapy. The most important adverse effect of the TMZ treatment regimen are thrombocytopenia and hematologic toxicity. In phase 2 clinical trials, these side effects are reported in 10–20% of patients. Radiation therapy is used to remove local microscopic cancer cells. All these microscopic cancer cells present in the form of brain tumor cannot be removed by surgery. Unfortunately, GBM cannot be treated easily because of its resistance to both chemotherapy as well as radiation therapy. Resistance mainly develop because of the unique biology of GBM cells. As a result, the effect of the traditional treatments get hindered through mechanisms including enhanced resistance to cell death as well as quick regeneration of cancer cells (Yalamarty et al., 2023).

1.3.4 Recurrent Glioblastoma and its Current Treatment Option

Glioblastoma multiforme (GBM) almost always reappears even after treatment with surgery, chemotherapy and radiotherapy (Park et al., 2010). Recurrence of glioblastoma mostly of the time results from a local continuous growth which is seen within the 2-3 cm from the border of the actual lesion. Recurrence of glioma has been seen at the original tumor location in above 90% of patients. Additionally, only in 5% patients multiple lesions have developed after treatment. Due to the formation of a new parenchymal lesion which is unable to show continuous growth patterns, dissemination or intra-ventricular spread, GBM may again reappear (Roy et al., 2015). Multiple treatments have shown effectiveness in specific recurrent glioblastoma patients. For instance: re-irradiation, re-treatment with bevacizumab, temozolomide or nitrosoureas and second surgery. To elaborate, re-irradiation can be applied

only in specific recurrent glioblastoma patients and the re-irradiation techniques include hypofractionated stereotactic radiotherapy, conventionally fractionated external radiotherapy and stereotactic radiosurgery. The most widely used systematic treatment is chemotherapy with nitrosoureas or temozolomide as well as antiangiogenic therapy with bevacizumab. In case of second surgery, it is only successful in patients with localized relapse in non-eloquent areas. In this type of patients it is possible to perform complete or subtotal resection of progressive tumor. In order to undergo second surgery, selected patients must have a good performance status. Also, patients need to have a relatively indolent tumor history that is measured as a prudential time from the first surgery to the second surgery (Pineda et al., 2023). However, the perfect treatment strategy for treating recurrent glioblastoma remains a subject of controversy. Thus, there is no standard treatment for recurrent glioblastoma in the present situation (Vaz-Salgado et al., 2023).

1.4 Clinical Trials of Glioblastoma

The search for alternative effective treatments for glioblastoma has not been successful so far. It is very essential to develop a better high-grade glioblastoma treatment (Shikalov et al., 2024). In recent times, clinical trials of the specific targeted and anti-angiogenic drugs are going on for the treatment of glioblastoma (Malhotra et al., 2015). Basically, clinical trials, a systematic process, discover the safety and effectiveness of drugs or devices in order to treat, prevent or diagnose a medical condition. There are 5 different phases of clinical trials including phase 0, phase I, phase II, phase III, and phase IV. Phase 0 or micro-dosing phase used to be performed only in animals. However, in recent times it is carried out in human volunteers so that the tolerability of dose or pharmacokinetics can be understood before administering in healthy individuals in phase I. In phase I trial, pharmacodynamics and pharmacokinetics effect of the drugs are checked (Kandi & Vadakedath, 2023). For example, Ketogenic diet is undergoing phase I trial as an adjuvant treatment for recurrent glioblastoma multiforme in order to check the safety of the diet (Yalamarty et al., 2023). In contrast, phase II trials mainly examine the efficacy of the new treatments. If the new treatments passes the phase II trial only then it will be allowed to undergo randomized phase III trial where investigation will be done on a large scale and safety will be assessed (Torres-Saavedra & Winter, 2022). For instance: the efficacy and safety of Rhenium Nano liposomes in recurrent glioblastoma are assessed in phase II trials. Moreover, phase III clinical trial, a pre-marketing phase, checks the safety and efficacy of drugs. For example, recently in the phase III trial of ongoing Glioblastoma Adaptive Global Innovative Learning Environment (GBM-AGILE), safety and efficacy of drug Multi-Kinase

Inhibitor drug is being examined in recurrent setting (Wang et al., 2021). Phase IV or Post-approval study designed to follow up patients for a longer period of time so that the probable drug-drug interaction as well as adverse reactions can be identified (Kandi & Vadakedath, 2023). For example: Bevacizumab is under phase IV clinical trial (Sinha et al., 2023).

1.5 Efficacy Endpoints

In case of the recurrent glioblastoma disease, clinical efficacy has seen only in a few systemic treatments and this has made treatment of GBM a clinical challenge (Di Nunno et al., 2021). In phase II clinical trials effectiveness of the novel drug or combination of the novel drugs are observed and main goal of this trial is to check the drugs in a full phase III trial. Usually, a well-established surrogate end point of the phase II trials shows the clinical efficacy when met and this further leads to the development of the drug. Assessment of the potential benefit of treatments, acceleration of the evaluation of risk benefit and clinical development are done by surrogate end-points. Time to progression (TTP), progression-free survival (PFS) and overall response rate (ORR) are the proposed surrogate end points for overall survival (OS). Among all the proposed surrogate end points, two common end points for glioblastoma multiforme (GBM) patients are six-month PFS as well as 12-month OS (Ballman et al., 2007). In the cancer clinical trial, OS is considered as gold standard end point. It plays a crucial role in identifying clinical effectiveness and cost effectiveness of recent intervention as well as it checks if it is possible to recommend for use in standard of care (Royle et al., 2023). PFS is the length of the time from beginning to the occurrence of progression of the disease or even death (Gyawali et al., 2022).

PFS and OS are closely interconnected in glioblastoma (Han et al., 2013). The percentage of the people achieving response including complete disappearance of lesions as well as reducing the total maximal tumor diameters by at least 30% or more is called ORR (Sachdev et al., 2022). In order to demonstrate efficacy of the treatment ORR plays a significant role as it is required for accelerated development of highly active anti-cancer therapies (Aykan & Özatlı, 2020; Oxnard et al., 2016). Even though OS is the gold standard in cancer treatment, only comparing OS difference between treatment arm results delayed approval of drugs. In order to speed up the drug approval process PFS and ORR can be used as surrogate end points to OS. Recently, in phase II clinical trials many promising targeted drugs are investigated. Thus, more improvements are necessary in clinical trial design and vast sample sizes as well as a greater

understanding of molecular subtyping are also required to get better outcome (Wang et al., 2021).

1.6 Aim of the Study

The main aim of this study is to help clinical trial examiners as well as cancer medication researchers to select appropriate efficacy endpoints and optimum cancer drug combination the phase II clinical trials of recurrent glioblastoma.

1.7 Objectives of the Study

- To determine the correlation between surrogate endpoints (PFS, ORR and DOR) and overall survival (OS) in phase II clinical trial of recurrent glioblastoma.
- To model the relationship among overall survival, progression free survival, overall response rate, wECOG, age, treatment Size and treatment agents through linear regression in phase II trials of recurrent glioblastoma.
- To study the impact of various treatment options on progression free survival, overall survival and overall response rate including combination of chemotherapy and targeted therapy.

Chapter 2

Methodology

2.1 Efficacy Endpoint and Predictor Variables

In clinical trials the primary efficacy endpoint is a clinical or laboratory outcome that is measured in an individual soon after randomization and after randomization these outcomes will allow one to test the primary hypothesis as well as help to examine the treatment effectiveness in comparison to its control (Follmann, 2005). First of all, the time from beginning of the treatment to occurrence of disease progression is called progression free survival (PFS) (Gyawali et al., 2022). Secondly, overall survival (OS) is the gold standard endpoint that is used to assess the clinical effectiveness of the experimental intervention for cancer treatment (Royle et al., 2023). Moreover, overall response rate (ORR) is patient percentage who have achieved complete response and partial response (Sachdev et al., 2023). In addition, duration of response is the time starting from the randomization to disease progression or death (Delgado & Guddati, 2021). Median value of PFS, OS and DOR in months were only taken into account. However, OS, PFS and DOR expressed in days or weeks were converted into months. Additionally, ORR expressed in percentage was only considered. Besides, median age was considered. As a predictor variable median age, treatment history, ECOG performance status, treatment size and targeted therapy were included.

2.2 Data Sources

We focused our search by using a single database, PubMed, as a source to help in assessing Phase II clinical trials of recurrent glioblastoma articles. We continue our search in PubMed using particular terms like 'Phase II clinical trial of recurrent glioblastoma' in order to narrow down our selection of relevant articles. This project is designed to get the desired efficacy endpoints from the initial 391 articles of Phase II recurrent glioblastoma clinical trial articles. Additionally, using a single database will simplify the process of data collection and management of data will also become much easier within a limited time period.

2.3 Inclusion and Exclusion Criteria

Particular parameters have been set to efficiently conduct the inclusion and exclusion process. Our first concern was to include only Phase II clinical trials of recurrent/metastatic/advanced glioblastoma articles. However, articles other than Phase II clinical trials including Phase I or III recurrent/metastatic/advanced glioblastoma were removed. In addition, Phase II clinical trials of recurrent/metastatic/advanced glioblastoma including surgery or radiation in the treatment plan were also excluded. We mainly used articles containing two or more efficacy endpoints. Moreover, overall survival (OS) and progression free survival (PFS) expressed in percentage were excluded as well. In the articles if PFS was missing then we considered time to progression (TTP).

2.4 Study Plan

The efficacy endpoints include PFS, OS, DOR and ORR. In our study, among the 391 articles we found 236 PFS, 225 OS, 214 ORR and 37 DOR. We will highlight two significant characteristics based on the mentioned efficacy endpoints. In the beginning our primary goal was to find out whether certain medications that are added in the treatment plan for the patients have any significant effect on the patient overcoming the ailment. Our next target was to find out the correlation between the different types of treatment strategies and effects of these treatments on the efficacy endpoints. Such as immunotherapy, combination of chemotherapy etc.

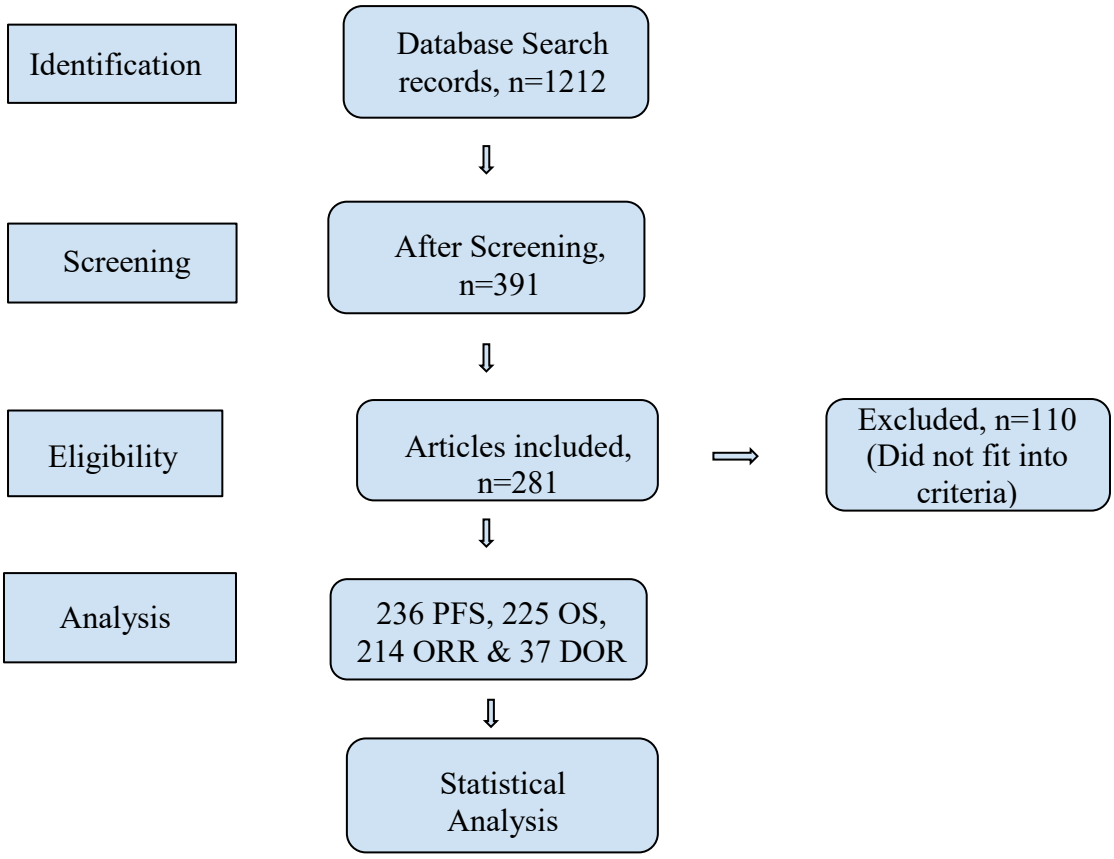

Figure 1: Study Plan (PFS, Progression Free Survival; OS, Overall Survival; ORR, Overall Response Rate; DOR, Duration of Response)

2.5 Statistical Analysis

A two-tailed welch t-test was performed. This t-test was performed to compare the OS among the treatment sizes and the comparisons among the progression free survival (PFS) were performed among the same treatment sizes. In order to find out a correlation among PFS, OS and age, Pearson correlation was used. A linear regression analysis was performed in order to predict variables and to find out the additional parameters. All the tests were conducted using Microsoft Excel 2016.

Chapter 3

Result

3.1 Dataset Overview

From the initial 391 studies, 281 met the inclusion criteria and consequently gathered in our study. The gathered information contain only phase II clinical trials of recurrent glioblastoma treated with chemotherapy (n = 105) and targeted therapy (n = 198) as a single agent or in combination. Trials with radiotherapy and surgery were excluded. Among the 391 studies there were 236 PFS, 225 OS, 214 ORR and 37 DOR.

Table 1: Summary table of the collected data set

Characteristics	N (Overall N = 391)	ORR[a] (95% CI)	PFS[a] (95% CI)	OS[a] (95% CI)
Previous Treatment				
Pretreated	277	9.6 (12.3, 16.3)	2.9 (12.3, 16.3)	8.1 (8.5, 9.6)
First line	4			
Treatment size				
1-Agent	163	7.6 (10.1, 15.1)	2.5 (2.7, 3.4)	8 (8.2, 9.4)
2-Agent	107	12.8 (13.7, 20.5)	3.6 (3.6, 4.7)	8.8 (8.7, 10.7)
3-Agent	12	25 (9.07, 28.3)	3.25 (2.2, 4.5)	7.2 (5.9, 10.1)
Treatment Type				
Chemotherapy	105	10.1 (10.2, 15.5)	2.9 (3.1, 4.4)	8.2 (8.2, 10.5)
Targeted Therapy	198	9.5 (12.8, 17.9)	3 (3.1, 3.7)	8.15 (8.4, 9.4)

[[a] Median value; ORR, Overall Response Rate; PFS, Progression Free Survival; OS, Overall Survival]

3.2 Correlation of Surrogate Endpoints with Overall Survival (OS)

3.2.1 PFS Correlation with OS

In this study, sample size of PFS and OS correlation pair is 226. According to our analysis, the Pearson correlation coefficient, r value is 0.48. It shows a moderate positive correlation between PFS and OS. In addition, the p value is <0.00001 which clearly indicates that the result is highly significant as the value is smaller than 0.05. Also, 95% CI values are 0.37, 0.57.

3.2.2 ORR Correlation with OS

In this study, sample size of ORR and OS correlation pair is 189. As per our study, Pearson correlation coefficient, r value is 0.14 and it clearly indicates that there is a weak positive correlation between ORR and OS. In addition, the p value is 0.047 which clearly indicates that the result is statistically significant as the value is smaller than 0.05. In addition, 95% CI values are 0.001, 0.28.

3.2.3 DOR Correlation with OS

In this study, sample size of DOR and OS correlation pair is 35. The Pearson correlation coefficient, r value is 0.19. It clearly indicates that there is a weak positive correlation between DOR and OS. In addition, the p value is 0.283 which clearly indicates that the result is not statistically significant as the value is greater than 0.05. Additionally, 95% CI values are -0.161, 0.502.

3.3 Regression Analysis

In our analysis, we have designed a full model and a reduced model to perform regression.

3.3.1 Linear Regression Analysis for Full Model

Table 2: Linear Full Model of OS

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	16.78	3.79	4.42	2.31E-05	9.26	24.30
mPFS	0.29	0.12	2.44	0.016	0.05	0.53
ORR%	0.02	0.02	1.40	0.16	-0.011	0.07
wECOG	-3.80	1.01	-3.73	0.0003	-5.82	-1.78
Treatment Size	-0.06	0.50	-0.12	0.90	-1.06	0.94
Targeted	0.66	0.64	1.03	0.303	-0.61	1.95
Age	-0.12	0.07	-1.81	0.07	-0.26	0.01

[mPFS, median Progression Free Survival; ORR, Overall Response Rate; wECOG, Weighted Eastern Cooperative Oncology Group]

The predicted equation derived using linear regression given below: OS = 16.78 + PFS × 0.29 + ORR × 0.029 - wECOG × 3.80 - Treatment size × 0.06 + Targeted × 0.66 - Age × 0.12

According to regression statistics, R square value is 0.23 and adjusted R square value is 0.2. The obtained adjusted R square value 0.2 indicates that the independent variable (mPFS, ORR, wECOG, Age, Treatment size and Targeted agent) could account for 20% of the account variability in mOS, considering the variable number. There was a marginal increase in the R square ($R^2 = 0.2$) value in comparison to the adjusted R square value (Adjusted $R^2 = 0.2$). The intercept of the regression model is 16.78 which indicates that the dependent variable (OS) will have a value of 16.787 when the independent variables including PFS, ORR, wECOG, Age, Treatment Size and Targeted Agent are equal to 0. In addition, mPFS and wECOG are the only significant explanatory variables as the p values for both the variables are smaller than 0.05. However, ORR, Age, Treatment Size and Targeted Agent were not found significant as their p value is much greater than 0.05.

3.3.2 Linear Regression Analysis for Reduced Model

Table 3: Linear Reduced Model of OS

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	7.36	0.76	9.60	1.19E-17	5.84	8.87
mPFS	0.58	0.11	4.88	2.45E-06	0.34	0.81
ORR%	0.008	0.01	0.49	0.62	-0.02	0.04
Treatment Size	-0.32	0.45	-0.70	0.48	-1.22	0.58
Targeted	0.07	0.41	0.18	0.852	-0.74	0.90

[mPFS, median Progression Free Survival; ORR, Overall Response Rate]

The predicted equation derived using linear regression given below:

OS = 7.36 + PFS × 0.58 + ORR × 0.008 - Treatment Size × 0.32 + Targeted × 0.07

In this model we only used OS, PFS, ORR, Treatment Size as well as Targeted Agents to see the linear relationship among these mentioned variables. The obtained adjusted R square value 0.13 indicates that the independent variable (mPFS, ORR, Treatment size and Targeted agent) could account for 13% of the account variability in mOS, considering the variable number. There was a marginal increase in the R square (R^2 = 0.15) value in comparison to the adjusted R squared value (Adjusted R^2 = 0.13). The intercept of the regression model is 7.36 which indicates that the dependent variable (OS) will have a value of 7.36 when the independent variables (PFS, ORR, Treatment Size and Treatment agent) are equal to 0. In addition, mPFS is the only significant explanatory variable as the p values for both the variables are smaller than 0.05. However, ORR, treatment size and targeted agents were not found significant as their p value is much greater than 0.05.

3.4 Comparison of Efficacy between Chemotherapy and Targeted Therapy

The PFS mean difference between chemotherapy and targeted therapy are 3.78 and 3.38 respectively. Here, we observed that there is a very little difference between the means of chemotherapy PFS and targeted therapy PFS. Also, the p value is 0.26 that clearly indicates that the obtained value is not statistically significant.

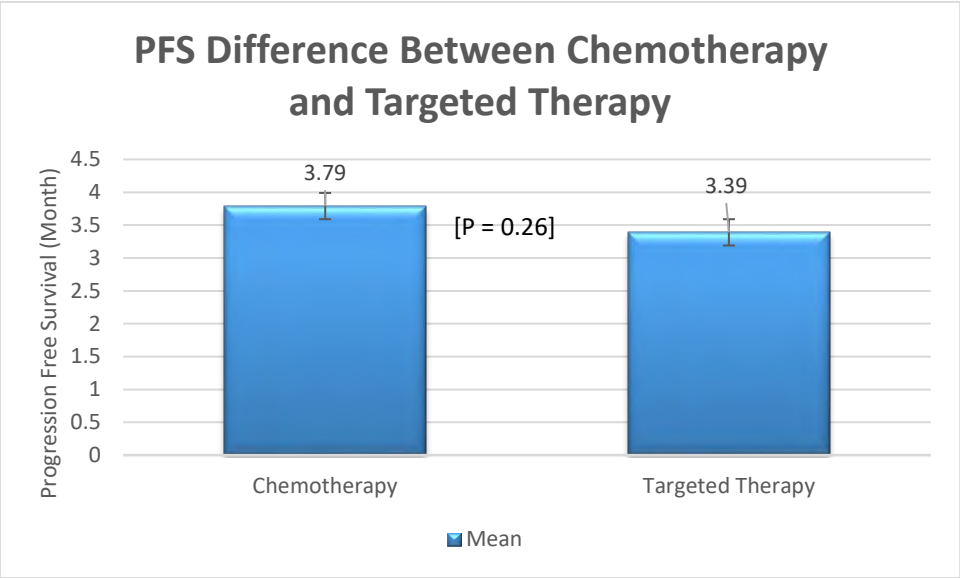

Figure 1: Impact of chemotherapy and targeted therapy on progression free survival (PFS). In the bar graph, Y-axis indicates the mean value of median PFS. Error bar indicates standard error.

In contrast, t test of OS for both chemotherapy and targeted therapy shows that means for chemotherapy and targeted therapy are 9.33 and 8.91 respectively. Here, we observed that there is a marginal difference between the means of chemotherapy OS and targeted therapy OS. Also, the p value is 0.51 which clearly indicates that the obtained value is not statistically significant.

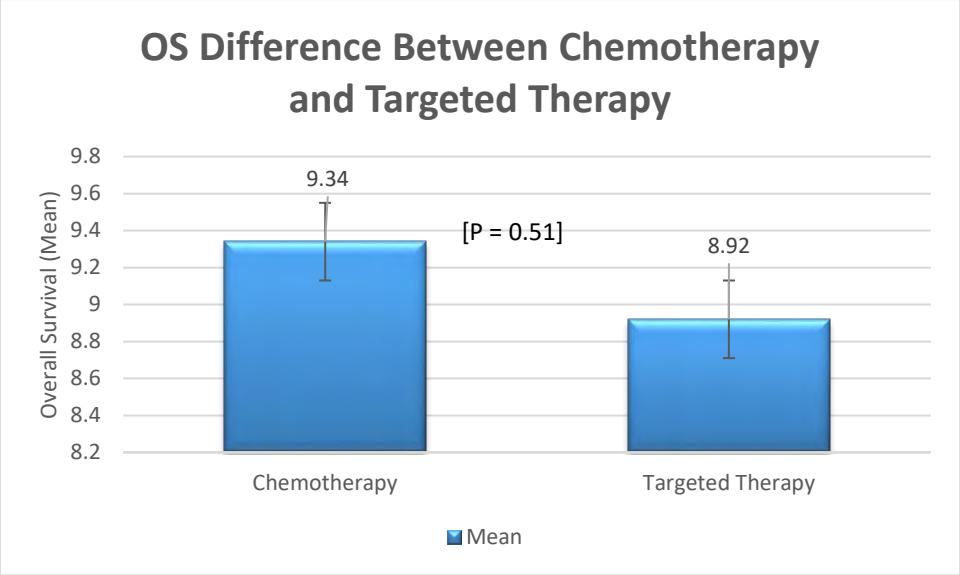

Figure 2: Impact of chemotherapy and targeted therapy on overall survival (OS). In the bar graph, Y-axis indicates the mean value of median OS. Error bar indicates standard error.

However, t test of ORR shows that means of ORR for both chemotherapy and targeted therapy are 12.85 and 15.36 respectively. Here, we notice that there is a significant difference between the means of chemotherapy ORR and targeted therapy ORR. Also, the p value is 0.17 which clearly indicates that the obtained value is not statistically significant.

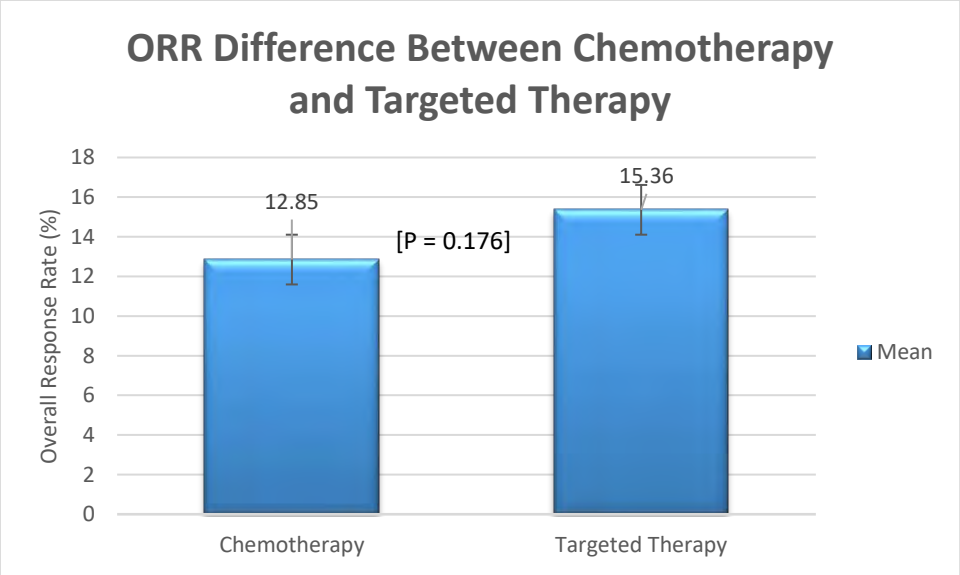

Figure 3: Impact of chemotherapy and targeted therapy on overall response rate (ORR). In the bar graph, Y-axis indicates the mean value of ORR. Error bar indicates standard error.

Chapter 4

Discussion

Glioblastoma is the most common as well as aggressive primary CNS tumor which is mainly associated with a poor prognosis (Chang et al., 2024; Vaz-Salgado et al., 2023). Basically, reappearance of a particular disease is the most common way of progression (Vaz-Salgado et al., 2023). There have been several different treatment agents that have been studied throughout the years for recurrent glioblastoma including cell checkpoint pathways, therapeutics targeting VEGF, other alkylating cancer agents etc. Even after performing multiple preclinical and clinical trials, effective treatment for recurrence of brain tumor or recurrent glioblastoma has not been discovered yet (Taslimi et al., 2021). We performed a pooled efficacy analysis of phase II clinical trials of recurrent glioblastoma to determine the effectiveness of treatments in patients with recurrent glioblastoma as well as to assess the effectiveness of medicine on the overall probability of survival.

As per our study, Pearson correlation was implemented to assess the correlation surrogate endpoints and OS, also to determine the degree to which the relation falls from -1 to +1. The correlation test is, "r = 0.48, 95% CI = 0.37-0.57, $p < 0.00001$" which suggests that a highly significant moderate positive relationship between PFS and OS. In contrast, we observed a weak positive statistically significant correlation (r = 0.19, 95% CI = -0.161-0.502), p = 0.004) between ORR and OS. Similarly, there is a weak positive correlation (r = 0.14, 95% CI = 0.001-0.28, p = 0.283) between DOR and OS as well but it is not statistically significant.

As per one study utilizing 91 clinical trials, there is a statistically not significant but strong positive relationship between OS and PFS (calculated weighted Pearson correlation = 0.70 and the weighted linear regression p-value = 0.49) (Han et al., 2013). On the other hand, in our analysis we observed moderate positive statistically significant correlation between PFS and OS. In agreement with our study, another study utilizing 16 clinical trials claimed that there is a moderate strong positive and statistically significant relationship between OS and PFS (weighted Pearson correlation = 0.64 and the weighted linear regression p-value = 0.007) (Ballman et al., 2006). Also, this study came to the conclusion that the relation between PFS and OS is strong in recurrent glioblastoma in comparison to newly diagnosed recurrent glioblastoma.

A study using 12 clinical trials claimed that the relationship between OS and ORR is moderate positive linear correlation but statistically not significant (calculated weighted Pearson correlation = 0.407 and the weighted linear regression p-value = < 0.0001) (Ellingson et al., 2023). In contrast, in our study we found that there is a weak positive statistically significant correlation between ORR and OS. In case of relationship between DOR and OS, a study utilizing 120 phase III trials shown that DOR and OS are highly correlated as there is a strong positive and statistically significant correlation between both the end points with calculated weighted Pearson correlation of 0.92 and the weighted linear regression p-value of < 0.0001. In contrast, as per our study utilizing phase II trials showed that there is weak positive and statistically not significant correlation between DOR and OS.

In our analysis, we have designed a full model and reduced model to perform regression analysis so that we can examine the relationship between two or more variables of interest. Also, we can find out the importance of significant variables as well as we can examine the overall predictive power of the model. In the case of the full model we have chosen all the potential covariates and predictor that might influence the outcome including mOS, mPFS, ORR, wECOG, Age, Treatment Size and Targeted Agent. All these variables would help us to understand their combined effect on the outcome. In our analysis for the full model we used 114 studies where we found that the R square value is 0.23 and adjusted R square value is 0.2. The obtained value clearly indicates that the independent variables including mPFS, ORR, wECOG, Age, Treatment Size and Targeted Agent could account for 20% of the account variability in the dependent variable median OS, considering the variable number. Also, the intercept of the regression model is 16.78 which indicates that when independent variables are equal to 0, only then the dependent variable (OS) will have a value of 16.78. Here, mPFS and wECOG are the only explanatory statistically significant variables. In contrast, as per one study utilizing 91 clinical trials states that R square value is 0.70 and no statistical significance observed where mOS considered as dependent variable and mPFS considered as independent variable (Han et al., 2013). Regression analysis on full model allowing us to understand that whether all the known variables has any effect on the treatment efficacy or not. In addition, full model is helping us to understand that whether treatment of recurrent glioblastoma getting affected by age or not. Our study predicted that there is an inverse relationship between the independent variable age and dependent variable mOS because the coefficient for age is -0.127 indicates that as the patients age increase, probability of survival of patients get decreases.

More specifically, the log odds of survival decrease by 0.127 for each additional year of age. Similarly, coefficient of wECOG also came negative (-3.80) which indicates that as the wECOG increases, the mOS decreases holding the other variables constant. As a result, worse performance status which means higher ECOG will lead to reduce survival time or reduce likelihood of survival. Likewise, in our study we obtain negative coefficient value (-0.066) for treatment size which means increasing treatment size will lead to decrease median overall survival. In contrast, coefficient value for median PFS (0.29), ORR% (0.029) and targeted (0.66) found positive. It clearly defines that the predictor variable is associated with increasing median PFS, ORR% and targeted drugs. To elaborate, 1 month of median overall survival increased by increasing progression free survival up to 0.29 month, 0.029% overall survival rate. Also, increasing targeted agent will also increase median OS.

Besides, in analysis of our reduced model we observed 171 studies from where we have only taken median PFS, ORR%, treatment size and targeted agent and mOS values. Here, mOS is the only dependent variable. This model exclude the variables (Age & wECOG) that may not have significant impact on the outcome and make the model easier to interpret. Additionally, intercept of the regression model is 7.32. This intercept value helps us to understand the desired outcome when no particular treatment or predictor is applied which particularly means when the independent variables including median PFS, ORR%, treatment size and targeted agent are equal to 0, the dependent variable (OS) will have a value of 7.32. Moreover, according to the reduced model, mPFS is the only significant explanatory variable because the p value is smaller than 0.05. On the other hand, ORR, treatment size and targeted agents were not found significant as their p value is much greater than 0.05. In this model we again found positive coefficient value for median PFS (0.58), ORR% (0.008) and targeted drugs (0.077).
Furthermore, in both regression analysis we obtain a positive value of intercept; it clearly shows that whenever the independent variables value get increased, value of median OS will also increase.

As per our study, the efficacy of chemotherapy drugs on recurrent glioblastoma patients demonstrated more effective outcomes in terms of OS and PFS. To illustrate, in the case of chemotherapy there was a drop with a narrow difference in mean PFS where the mean PFS are 3.78 and 3.38 for chemotherapy drug and targeted therapy respectively. The value indicates that patients receiving chemotherapy have longer time before progression of disease in comparison to the patients who are receiving targeted therapy. So, chemotherapy is seems

likely to be more effective than targeted therapy in delaying progression of aggressive tumor in the CNS of the glioblastoma patient being studied. However, the p value (0.26) for PFS clearly shows that the obtained value is not statistically significant which means the observed difference may result due to random cancer. Similarly, the mean OS of chemotherapy and targeted therapy was 9.33 and 8.91 respectively. Mean OS between chemotherapy and targeted therapy has slight differences as well which means patients receiving chemotherapy survive longer than the patients who are receiving targeted therapy. Here, the obtained p value (0.17) is not statistically significant as well that defines that the difference could be due to random reason, no real advantage is actually proven for chemotherapy over targeted therapy. On the other hand, we found different results in the case of ORR as the mean ORR of targeted therapy (15.36) was higher than chemotherapy (12.85). There is a greater increase in the mean ORR of targeted therapy in comparison to chemotherapy. This shows that a greater percentage of patients receiving targeted therapy experience better tumor response like shrinkage of tumor or disappearance of tumor in comparison to patients receiving chemotherapy. However, p value of ORR was 0.17 which indicates the obtained value was not statistically significant. It means the difference between mean ORR of targeted therapy and chemotherapy is not meaningful, it may occur due to any random cause. Apart from our study another study utilized 42 studies to conduct Bayesian meta-analysis to see effectiveness of chemotherapy and targeted therapy in recurrent glioblastoma. This study showed that chemotherapy like: lomustine monotherapy is the best treatment for the patients in comparison to targeted therapy. However, this study assumed that combination of chemotherapy (e.g., Lomustine) and targeted therapy (e.g., Bevacizumab) showed better ORR and better PFS but it is unable to improve OS and has greater possibility to show adverse effects (McBain et al., 2021). Lastly, the opportunity to use phase II clinical trials of recurrent glioblastoma, conducted on patients of different age group, gender, ethnicity as well as comparing efficacy endpoints between chemotherapy and targeted therapy is the major strength of our study which enabled us to limit some of the known drawbacks of a retrospective observational study.

Chapter 5

Conclusion

The pooled efficacy analysis of phase II clinical trials was performed to see the effectiveness of existing treatments on recurrent glioblastoma. Our research will help the healthcare professionals to choose appropriate medicine for recurrent glioblastoma patients as well as to avoid misinterpretation. Our study clearly shows that treatments including chemotherapy and targeted therapy have direct correlation with the efficacy end points (PFS, OS, ORR and DOR). Findings of our study shows that mean PFS and OS of chemotherapy is greater in comparison to targeted therapy. However, an unexpected result obtained for targeted therapy as ORR is much higher in case of targeted therapy than chemotherapy. Remarkably, expected statistical significance was not found in both chemotherapy and targeted therapy as p value of PFS, OS and ORR was greater than 0.05 in both cases. So we can say that chemotherapy is more effective for recurrent glioblastoma treatment as it can reduce the progression of tumor more effectively and enhance the survival rate of the patients as well. Conversely, using only targeted therapy is not as effective as chemotherapy. We can assume that combination of both chemotherapy and targeted therapy might give better results in reducing the brain tumor progression as well as enhance the survival rate of the glioblastoma patient. We can understand that our analysis may not have the desired accuracy as we would require vast datasets from multiple phase II clinical trial studies. Additionally, our analysis is somewhat limited as we take into account only recurrent or metastatic glioblastoma as well as we excluded all the phase I or III trials and radiotherapy or surgery used in recurrent glioblastoma. As a consequence, the relationship between efficacy endpoints could differ significantly. Therefore, further studies with a larger dataset may validate our findings.

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