A Review on Bevacizumab for the Treatment of Glioblastoma

By

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

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my/our 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.
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The thesis/project titled "A Review on Bevacizumab for the Treatment of Glioblastoma" submitted by Nafisa Tabassum Moon (19346064) of Summer 2019, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.)

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Ethics Statement

This review article maintains all the authenticity. For accomplishing the authenticity, I avoid any kind of plagiarism and ensure the citation accurately as well as avoid any kind of biased evaluation. Moreover, this study did not harm any types of patients or people as this study did not involve any human participants.

Abstract

Background: A targeted drug therapy like bevacizumab also known as monoclonal antibody used now-a-days in the treatment of glioblastoma which contributes significantly in the progression free survival.

Purpose: The goal of this review article was to assess the effectiveness and safety of a targeted therapy drug like bevacizumab, in glioblastoma patients and monitor their progress or improvement through observing the drug's available data.

Method: The article was searched by using all the associated terms for bevacizumab and glioblastoma through electronic databases such as PubMed, Web of science and Embase. A comprehensive analysis was conducted on all the relevant studies.

Result: Clinical trials and articles have demonstrated that bevacizumab can significantly improve the progression free survival rate of PFS for the glioblastoma patients but its effect on overall survival is still unclear. Both single and combination-based bevacizumab therapy are beneficial for the glioblastoma and enhance the patient's quality of life.

Keywords: Bevacizumab, Glioblastoma, Anti-angiogenesis, VEGF.

Dedication

First of all, this project is dedicated to my beloved father who always guides and inspires me with his wisdom and helps to find out my best version of me. Every success is tribute to those values he rooted in me, something that would make him proud.

Furthermore, a special dedication to my mother who passed away 22 years ago from a brain tumor. I hope she is watching this from heaven and feeling proud of me.

Acknowledgement

I am thankful to Allah that I was able to select pharmacy as my area of study. Without his mighty blessings I could not have completed this project as well as not be able to achieve my Bachelor's degree in Pharmacy.

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List of Acronyms

GBM	Glioblastoma
PFS	Progression Free Survival
OS	Overall Survival
VEGF	Vascular Endothelial Growth Factor
IV	Intravenous Infusion
RR	Response Rate
PR	Partial Response

Chapter 01

Introduction

1.1. Background Information

Glioblastoma (GBM) is the most common and aggressive malignant brain tumor and the survival time for these patients is 1-2 years (Stupp et al., 2005a). Despite improvements in therapeutic approaches the prognosis is still poor (Clark et al., 2012). Current standard treatment includes adjuvant radiation therapy (RT), chemotherapy with temozolomide (TMZ) and maximal safe surgical resection (Sherwood et al., 1971).

However, the median survival for GBM patients is still only 12-24 months and less than 10% of patients will survive 5 years after diagnosis which emphasizes how urgently new treatment approaches are needed (Stupp et al., 2009a).

Angiogenesis is the process in the growth of cancer which involves a variety of proteins and receptors including vascular endothelial growth factor (VEGF) and VEGF receptor that have been identified as targets for anti-cancer treatment (Tai Zhang & Qing Xin, 2021).

Bevacizumab is humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), blocking VEGF and preventing it from binding to VEGFR and it has been included analysis in various trials and used in the treatment of various cancer such as renal cancer, non-small-cell lung, breast cancer, ovarian cancer and colorectal cancer, including recurrent glioblastoma (GBM) (Stupp et al., 2005).

Bevacizumab was approved by the Food and Drug administration as a single agent for the patients with recurrent GBM (Cohen et al., 2009). The latest findings from a phase III trial indicate a

notable enhancement in progression free survival (PFS) when bevacizumab is incorporated into the standard treatment of radiation therapy (RT) alongside concurrent and adjuvant temozolomide for newly diagnosed glioblastoma (Gilbert et al., 2014). Prior studies comparing bevacizumab with bevacizumab plus irinotecan or bevacizumab plus lomustine indicated that bevacizumab may be the primary mediator of the anti-glioblastoma action on recurrent GBM (Friedman et al., 2009a). Bevacizumab produced conflicting outcomes with regarding to PFS and OS in contrast to several other anti-VEGF medications that were used in some major RCTs such as cediranib (VEGF inhibitor), nivolumab (anti-VEGF neutralizing antibody), regorafenib (VEGF-TKI), aflibercept (soluble VEGFR) (Tai Zhang & Qing Xin, 2021).

This review focused on the outcome of the bevacizumab vs some specific cytotoxic treatment for the patients with glioblastoma or recurrent glioblastoma such as lomustine, nivolumab, fotemustine, pembrolizumab and TRC105, etc. (Tai Zhang & Qing Xin, 2021).

1.2. What is bevacizumab?

A humanized monoclonal antibody directed against vascular endothelial growth factor is called bevacizumab (Gerriets & Kasi, 2024). Bevacizumab plays a significant role in the treatment of glioblastoma. It is also used to treat others cancer as well such as breast cancer, metastatic colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, cervical cancer, ovarian cancer, fallopian tube, metastatic renal carcinoma and primary peritoneal cancer (Gerriets & Kasi, 2024). In cancer treatment bevacizumab is used to prevent the growth of malignant cell and the formation of new blood vessel by inhibiting angiogenesis and microvascular expansion (Jain et al., 2007). Usually, bevacizumab is used in combination with other chemotherapeutic drugs

(Friedman et al., 2009b). Bevacizumab is authorized for use a single agent in patients with glioblastoma that is advancing and who have received previous therapy (Gerriets & Kasi, 2024).

Through intravenous infusion (IV) bevacizumab is administered. There are two different dosage forms for bevacizumab which is 4 ml and 16 ml solutions containing 100 mg and 400 mg (Bender et al., 2008).

If the initial infusion is well tolerated, then the next infusion should be given over e period of 60 minutes after the initial 90 minutes infusion (Gerriets & Kasi, 2024). If the patients are able to endure the 60-minute infusion, then more infusion can be administered over a period of 30 minutes (Taira et al., 2022). Numerous different dose schedules exist depending on the type of cancer being treated; most fall within the range of 5 mg to 15 mg/kg body weight on a cyclical treatment plan. (14 or 21 days) (Taira et al., 2022).

1.3. What is glioblastoma?

Gliomas are the most prevalent primary brain tumors in adulthood (Buckner, 2003). The world health organization's classify gliomas into low, high and intermediate scale (Louis et al., 2007). Pathological grade corresponds to a number between one and four (Norden et al., 2008). A poor prognosis is associated with high - grade gliomas (HGG) (Buckner, 2003). Glioblastoma, also referred to as grade IV gliomas, has a 15-month median survival rate in treated patients (Gil-Gil et al., 2013a). Vascular endothelial growth factor (VEGF), a protein that stimulates the creation of new blood vessels (the process of angiogenesis) is also abundant in glioblastomas, making them extremely vascular (Hicklin & Ellis, 2005).

1.4. Objective of the study

Studying bevacizumab effectiveness and safety in the patient population is the main goal of review on the drugs used in the glioblastoma treatment. Overall survival rate, progression free survival, radiographic response rate, adverse effects and quality of life measure are considered key endpoints or outcomes. Furthermore, this review article may help to evaluate particular patient subgroups to find out effective predictors of bevacizumab therapeutic response. Other objectives include Biomarker associated with or linked to angiogenesis or other related pathways, examining possible bevacizumab resistance mechanisms and evaluating how it affects neurological functions and symptoms management.

1.5. Rationale of the Study

The importance of studying bevacizumab in the treatment of glioblastoma to identify the mechanism of action in its anti-angiogenic agent. A statistic about clinical trials have shown notable improvement of 3-5 months in progression-free survival rates when compared to conventional therapy alone (Norden et al., 2008). Since glioblastoma are highly vascularized tumors, inhibiting angiogenesis may slow the growth of the tumor and maybe enhance patients' outcomes. This study is significant because glioblastoma is a brain cancer that is aggressive as well as incurable and it is critical to discover effective treatments to extended survival and enhance quality of life. Bevacizumab can inhibit VGEF, which can prevent the growth of new blood vessels in the tumor microenvironment. This can have anti-tumor effects as well as a reduction in tumor vascularity and edema. Promising outcome from early phase clinical trials have been observed including radiographic response and clinical benefit in a subgroup of patients with recurrent GBM. Moreover, combining bevacizumab with other targeted or cytotoxic drugs is a unique way to

enhance the drugs anti-tumor effect. Combination therapy approaches may improve treatment outcomes for individuals with GBM by targeting multiple pathways associated to glioma-genesis and tumor growth.

Bevacizumab treatment-based studies represent a logical and evidence-based strategy to filling a gap in the treatment of this difficult disease. Bevacizumab's potential role in improving outcomes for patients with GBM is being further explored through rigorous clinical investigation including randomized controlled trials translational research efforts. This provides hopes for improved therapeutic in the fight against this devastating malignancy.

Chapter 02

Methodology

Based on the recommended reporting elements (preferred reporting items) this review was conducted. “PubMed”, “Embase” and “Web of Science” were thoroughly searched to find out any available material up to 2022. I used to look up the following search terms: bevacizumab and glioblastoma and clinical trials, review article and bevacizumab and glioblastoma, recurrent and bevacizumab, combination therapy and bevacizumab and high-grade glioma.

Chapter 03

Mechanism Of Action

The recombinant humanized monoclonal immunoglobulin GI (IgGI) antibody bevacizumab, which has a molecular weight of 149 kDa as well as it mainly composed of human sequences with a tiny amount of murine sequences (7% murine sequences and 93% human sequences) (Gil-Gil et al., 2013b). Bevacizumab exhibits strong and high affinity for all isoforms of human VEGF and preferentially binds to them as well as it neutralizes the biological action of VEFG by sterically preventing VEGF's binding to its receptors, VEGFR-1 and VEGFR-2 on the endothelial cell's surface (Gil-Gil et al., 2013b). Tyrosine phosphorylation is induced normally by receptor activation and the consecutive sequence of signal transduction event that evokes mitogenic and pro- survival activity signal upon receptor activation in the vascular endothelial cell (Gil-Gil et al., 2013c).

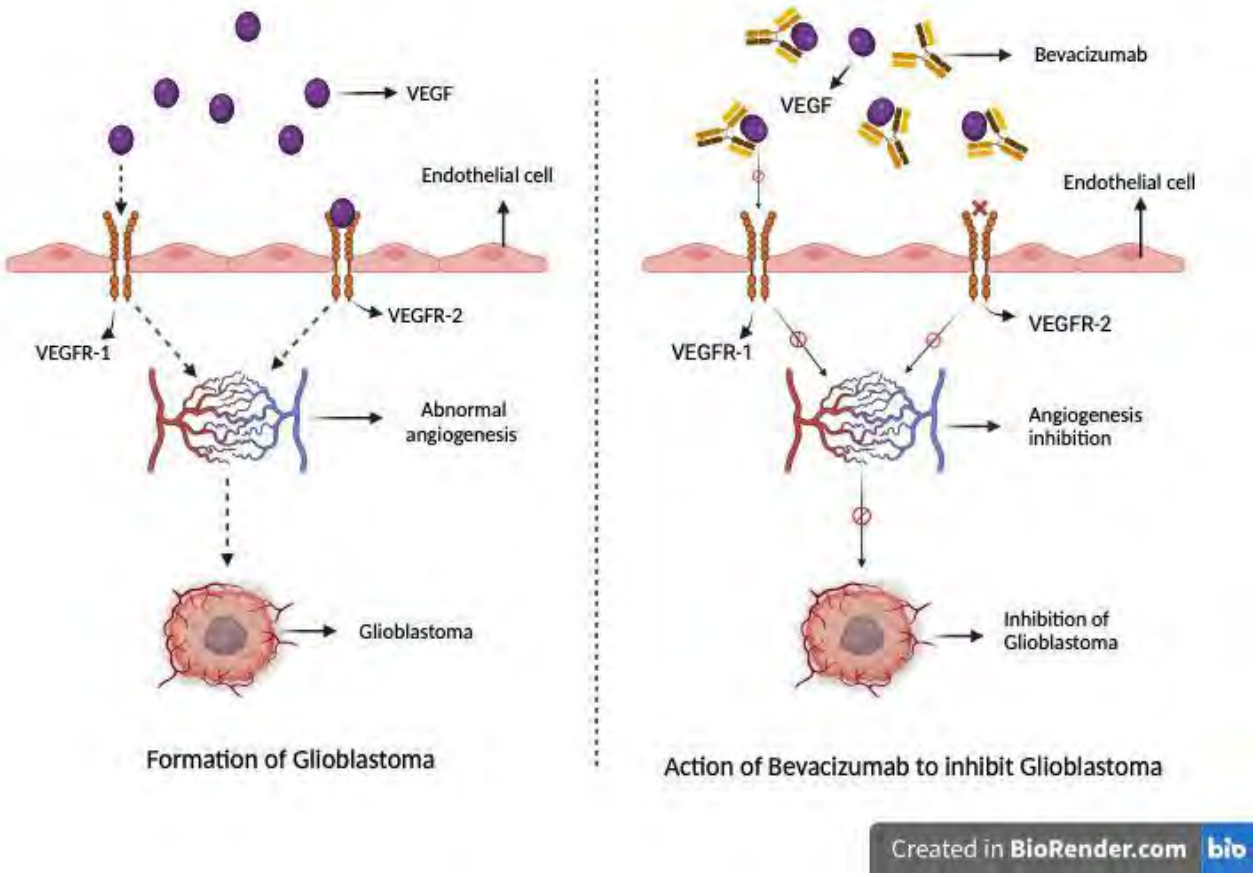

Figure 1: Mechanism of Action of Bevacizumab

It is well known that glioblastoma is one of the most vascularized tumors in humans (Gilbert et al., 2014). Glioblastoma is known to release a large range of proangiogenic factors, including VEGF from its cell (Gil-Gil et al., 2013b). In particular VEGF is essential for controlling blood brain barrier vascular permeability and angiogenesis (Louis et al., 2007).

It is one of the reasons these individuals have severe morbidity since it causes peritumoral edema and promotes vascular permeability (Gil-Gil et al., 2013b). VEGF is bound by bevacizumab, which specially prevents VEGF from interacting with the target receptors VEGFR-1 and VEGFR-2 on endothelial cell surface (Gil-Gil et al., 2013a). By blocking VEGF's biological activity, tumor angiogenesis is reduced which in turn vasogenic brain edema and tumor growth (Hicklin & Ellis,

2005). Widespread anti-tumor action was observed in human malignancies such as those of breast cancer, colon cancer, pancreas cancer and prostate cancer when bevacizumab or its parental murine antibody was administered to cancer xenotransplant model in naked mice (Jain et al., 2007). Reduced microvascular permeability and inhibited the spread or progression metastatic illness were observed (Jain et al., 2007).

Chinese hamster ovary mammalian cell expression system is used to manufacture bevacizumab by recombinant DNA technology (Mould & Sweeney, 2007). This is found in a nutrient medium that contains gentamicin, an antibiotic (Mould & Sweeney, 2007). Certain viral inactivation and removal procedures are part of the method which is used to purify bevacizumab (Mould & Sweeney, 2007). The final product has ≤ 0.35 ppm gentamicin (Mould & Sweeney, 2007).

For the treatment of metastatic colorectal cancer in conjugation with cytotoxic chemotherapy, the first anti VEGF therapeutic bevacizumab approved by the FDA in 2004 and EMA in 2005 (Hurwitz et al., 2004).

Subsequently FDA authorized its use for the treatment or management of metastatic renal carcinoma, metastatic breast cancer, advanced ovarian cancer and advanced non -small lung carcinoma (Ranpura et al., 2010).

Chapter 04

Pharmacokinetics

The bevacizumab pharmacokinetics (PK) data are obtained from multiple clinical trials. These trials are Conducted on patients who had solid tumors (Bender et al., 2008). Intravenous infusion was administered for bevacizumab in all the clinical trials. Based on the patient's tolerability the infusion rate of bevacizumab is set at a 90 minutes initial infusion duration which can be lowered to 60 minutes for subsequent infusions and 30 minutes for third and subsequent infusions (Gil-Gil et al., 2013b).

Parameter	Effect	Reference
Absorption	According to PK research, bevacizumab takes 84 days to reach 90% of steady state concentration and it follows linear pharmacokinetics.	(Hummel et al., 2022)
Distribution	Through a meta-analysis the identification was that males have a bigger core volume of distribution than females (2.93 L for a female and 3.29 for a male) after accounting body weight as well as the range that has been reported for IgGs and monoclonal antibodies of others. The most important factors to explain interpatient variability for CL and V were body weight and gender. Male patients exhibited a larger V (>20%) than female patients as well as CL for men 26% faster than women after accounting body	(Gil-Gil et al., 2013a)

	weight. The distribution pattern of bevacizumab was shown to be compatible with the tissue distribution of humanized IgG1 monoclonal antibodies. Bevacizumab had low distribution for extravascular and limitations for the tumor vasculature. When bevacizumab and anti-neoplastic agents given together the peripheral value was typically measured 1.69 L for female patients and 2.35 L for male patients.	
Metabolism	Bevacizumab's metabolism is most likely the same as that of endogenous antibodies such as IgG, and involves target mediated elimination by VEGF expressing cells as well as non-specific elimination pathways through proteolytic catabolism. Therefore, it has no effect on the liver's drug metabolizing enzyme activity.	(Valeriets, 2023)
Elimination	0.23 L per day is the average or mean clearance. Men have a roughly 26% greater clearance than women after correcting the body weight. Bevacizumab clearance varies according to body weight, sex and tumor burden. 20 days is the estimated half-life. Reduced alkaline phosphatase and increased albumin cause a decrease in clearance.	(Valeriets, 2023)

After analysis the all-clinical trial it is found that bevacizumab's acting was defined by a low CL, a limited Vc, and a long elimination half-life. This makes it possible to maintain the bevacizumab plasma levels for target therapeutic (Mould & Sweeney, 2007).

Chapter 05

Adverse effect

The National Cancer Institute Common Terminology Criteria for Adverse Events lists the following major adverse effects that are associated with bevacizumab alone for the glioblastoma treatment: hypertension, intracranial hemorrhage, proteinuria, wound healing complications, venous thromboembolic effects, gastrointestinal perforation (Narita, 2013). The proportions of these events that were all grade / ≥ grade 3 effects were 0-3% / 0% (ICH), 12.6% - 35.7% / 4.2-16% (HT), 2.1%-41.9%/ 0-3.2% (proteinuria), 3.2-16.0%/ 2.0-12. 6% (VTE) and 0-6.0%/0-2.4% (wound healing complications) respectively (Friedman et al., 2009a) (Chamberlain & Johnston, 2010).

There are also some other side effects such as fatigue, headache, pyrexia, seizures, cardiac failure, diarrhea, nausea, vomiting, peripheral edema, constipation, neutropenia, hyperglycemia and lymphopenia. Gastrointestinal proliferation is the uncommon or rare side effects for the glioblastoma treatment (Narita, 2013).

According to earlier research, there can be as much as 30% of different types of hemorrhage such as epistaxis, gingival hemorrhage, ICH, conjunctival bleeding, infusion site bleeding and blood associated with urine (Friedman et al., 2009b) (Nagane et al., 2012).

Hypertension: Cardiac ischemia, ICH and myocardial infarction are caused by HT which is the most frequent adverse effect in bevacizumab treated patients. According to a recent meta-analysis, patients who receive bevacizumab experienced occurrences of both 3-4 grade (23.6%) and all grade (7.9%) HT as well as the high-grade hypertension relative risk (RR) was 5.3 (P> 0.001) (Ranpura et al., 2010).

Proteinuria: One common side effect of VEGF is proteinuria. This side effect increases the risk of hypertension, cardiovascular disease and renal failure (Wu et al., 2010). The damage to the glomerular endothelium caused by bevacizumab which is responsible for the inhibition of the VEGF (vascular endothelial growth factor) (Eremina et al., 2008). This is the main reason for proteinuria (Eremina et al., 2008). A meta-analysis recently conducted found that 2.2% of patients who are receiving bevacizumab experienced grade 3-4 proteinuria with a relative risk of 4.8 (Wu et al., 2010). Proteinuria is the side effect which is associated with the bevacizumab treatment in the purpose of increasing risk with high doses and low doses of bevacizumab as well as the relative risk is 2.2 and 1.4, respectively (Zhu et al., 2007). Patients who need dialysis or who have identified with prolonged nephrotic syndrome even after stopping bevacizumab, close blood pressure monitoring, examinations of blood pressure and urine testing are required (Zhu et al., 2007). Bevacizumab doses should either be stopped or lowered if grade 3-4 proteinuria is seen (Zhu et al., 2007).

Intracranial hemorrhage: Patients with malignant brain tumors may experience ICH, which could be fatal (Velander et al., 2012). Intertumoral bleeding is the main cause of ICH. After reviewing case studies of cancer patients, found that up to 10% of patients have the risk of developing ICH (Velander et al., 2012). All cancer patients can experience ICH. The most common cancer types where the ICH arises naturally include glioblastoma, lung cancer, choriocarcinoma, breast cancer, renal cell carcinoma, oligodendroglia tumors, thyroid carcinoma and melanoma (Narita, 2013). After analyzing the multiple clinical trials, it is found that ICH is occurred in 1%

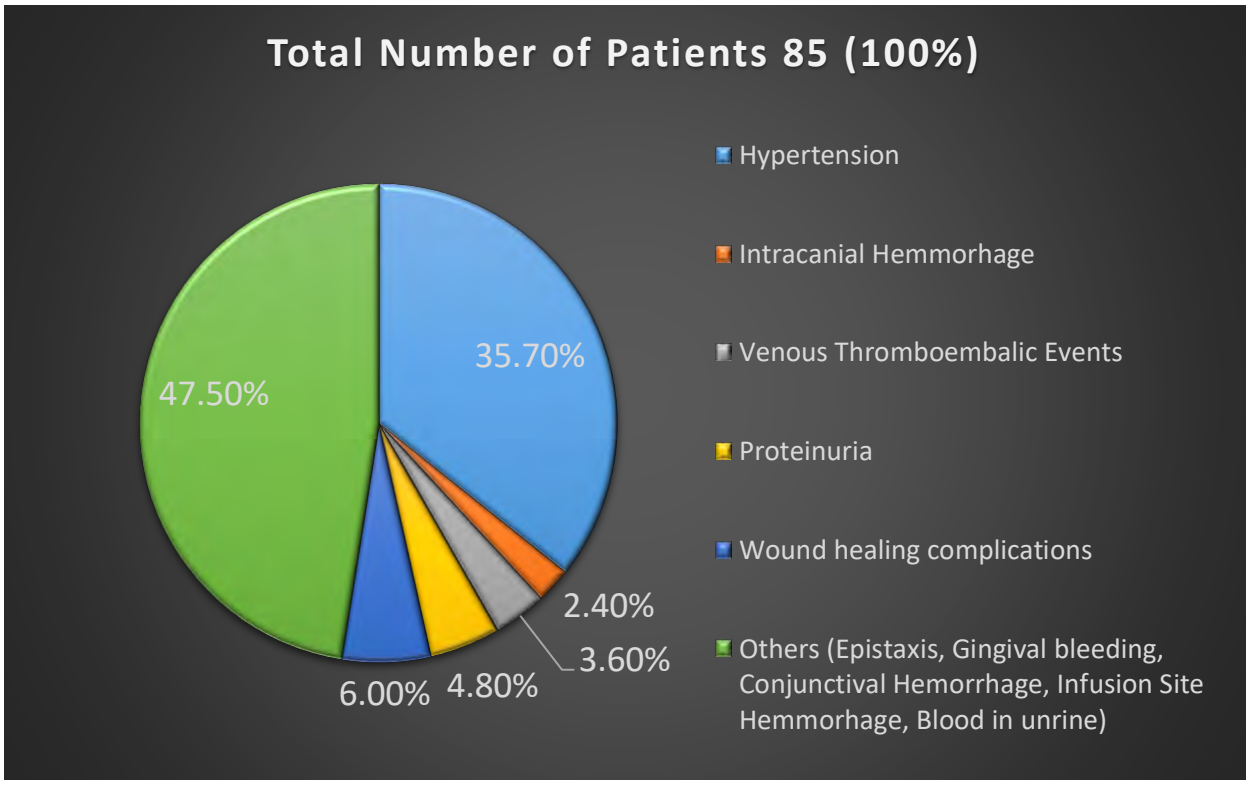

Figure 2: Pie Chart of Adverse Effects

of patients with glioblastoma who did not receive bevacizumab treatment and occurred in 0.8-3.3% of patients who receive the bevacizumab for the glioblastoma treatment (Besse et al., 2010). After going through more articles, I also found that ICH can occur for both groups of the patients who receive the treatment of bevacizumab or not (Velander et al., 2012). These results concluded that for malignant brain tumors bevacizumab is not contradicted.

Wound healing complications: The use of bevacizumab both before and after surgery may raise the risk of complications related to wound healing because vascular endothelial growth factor (VEGF) is crucial for healing the wounds after surgery (Gordon et al., 2009). It is recommended that it's better for a patient to wait a minimum of 6-8 weeks after stopping bevacizumab treatment before undergoing surgery as the medications have a half-life of 3 weeks or 20 days (Gordon et

al., 2009). It is also recommended that to avoid a higher risk of wound healing complications bevacizumab should not be started immediately after surgery for four weeks (Clark et al., 2011).

Venous thromboembolic effects: The risk of VTE was found to be considerably higher for those who take bevacizumab for the glioblastoma treatment (RR = 1.3) (Narita, 2013). There is no difference in risk between the patients who were treated with bevacizumab with doses of 2.5 and 5.0 mg/kg per week (Nalluri et al., 2008).

From a study it is found that malignant glioma patients with a 2-year cumulative incidence of VTE of 7.5% as well as among these patients about 55% who have been diagnosed with VTE after 2 months of the surgery (Semrad et al., 2007) However glioblastoma and malignant brain tumor patients have a greater risk with developing VTE.

Chapter 06

Result:

Name of the study	Intervention	Study design	Patients n	Baseline (Overall survival at 6 months)	Endpoint (Overall survival at 18 months)	P value	IDH status, n (%of tested)	MGMT status, n (% of tested)
(Brandes et al., 2019)	Bevacizumab 10mg/kg + Lomustine (CCNU) 90mg/m	Randomized Phase II clinical Trials; Age= 56 (30-74) years	n = 61 Male = 44 Female=17	OS was 6.4% (95% CI; 5.1-8.1; HR= 1.04)	OS was 4.7% (95% CI; 0.9-13.7)	No P values are reported, and 95% confidence Intervals are shown	/	Unmethylated 26/61 (43%), methylated 11/61(18)
	Lomustine 90mg/m^2 (CCNU) + Placebo	Age= 58.5 (36-74) years	n= 62 Male= 45 Female = 17	OS was 5.5% (95% CI; 3.9-7.2)	OS was 9.4% (95% CI; 3.1-20.1)		/	Unmethylated 25/62(40), methylated 12/62(19%)

Table 1: Summary of clinical trial to observe the efficacy of Bevacizumab & Lomustine

Name Of the Study	Intervention	Study Design	Patients n= 369	Baseline (Overall survival at 6 months)	Endpoint (Overall survival at 18 months)	P value	IDH status, n (%of tested)	MGMT status, n (% of tested)
(Reardon et al., 2020)	Bevacizumab	Randomized Phase III clinical trial Age = 55(22-76)	n= 185 Male= Female= 66 (36%)	78.2% (71.2-83.6); HR = 1.04; (95% CI, 0.83-1.30)	21.6% (15.8-28.0); HR = 1.04; 95% CI, 0.83-1.30	P= 0.76	/	Unmethylated 67/185(36.2%), methylated 42/185(22.7%), not done /unknown 76
	Nivolumab	Age = 55.5(22-77)	n= 184 Female= 68(37%)	72.3% (65.2-78.2); HR = 1.04;(95% CI, 0.83-1.30)	21.7% (16.1-27.9); HR = 1.04; (95% CI, 0.83-1.30)		/	Unmethylated 59/184(32.1%), methylated 43/184(23.4%), not done / unknown 82

Table 2: Summary of clinical trial to observe the efficacy of Bevacizumab & Nivolumab

Name of the study	Intervention	Study design	Patients n= 91	Baseline (Overall survival at 6 months)	Endpoint (Overall survival at 18 months)	P value	IDH status, n (%of tested)	MGMT status, n (% of tested)
(Brandes et al., 2016)	Bevacizumab 10mg/kg	Phase II, randomized, non-comparative study. Age = 59(37-74) years	n = 59 Male= 39 (66%) Female= 20 (34%)	OS was 62.1% (95% CI; 48.4-74.5)	21.6% (15.8-28.0)	No P values are reported, and 95% confidence Intervals are shown	/	Unmethylated=85%
	Fotemustine 75mg/m^2	Age= 56 (22-78)	n=32 Male=23 (72%) Female= 9	OS was 73.3% (95% CI; 54.1-87.7)	21.7% (16.1-27.9)		/	Methylated =87.5% Unmethylated= 50%

Table 3: Summary of clinical trial to observe the efficacy of Bevacizumab & Fotemustine

Name of the study	Intervention	Study design	Patients n = 88	Baseline (Overall survival at 6 months)	Endpoint (Overall survival at 18 months)	P value	IDH status, n (%of tested)	MGMT status, n (% of tested)
(Nayak et al., 2021)	Bevacizumab + Pembrolizumab	Randomized Phase II and biomarkers study	n = 50 Male = 35 (70%)	79.7% (95% CI; 69.2,91.7)	16.9% (95% CI; 9.0, 31.7	P= 0.87	Mutant 8(16.0%), wild typed 35(70.0%), unknown 7(14.0%)	Unmethylated 17(34.0%) Methylated 20(40%), unknown 13(26.0%)
	Pembrolizumab	Age = 55(42-65) years	n= 30 Male = 19 (63.3%)	70.0% (55.4, 88.5)	23.3% (12.2, 44.6	/	Mutant 4 (13.3%), wild type 21 (70.0), unknown 5 (16.7%)	Unmethylated 10 (33.3%), Methylated 9 (30.0%), unknown 5 (16.7%)

Table 4: Summary of clinical trial to observe the efficacy of Bevacizumab & Pembrolizumab

Name of the study	Intervention	Study design	Patients n	Baseline (Progression free survival)	Endpoint (Overall survival)	P value	IDH status, n (%of tested)	MGMT status, n (% of tested)
(Galanis et al., 2022)	Bevacizumab 10mg/kg + TRC105 10mg/kg	Randomized Phase II trials Age = 58.5 (31-86) years	n = 52 Female = 17 Male = 35	PFS rate 2.9 % (95% CI; 2.76-4.86) months	OS was 9.7% (95% CI; 6.74-11.53) months	PFS P= 0.51	/	/
	Bevacizumab Alone 10mg/kg	Age= 56.0 (32-75) years	n= 49 Female=12 Male= 37	PFS was 3.2% (95% CI; 2.60-4.63) months	OS was 7.4% (95% CI; 6.54-12.7)	OS P= 0.81	/	/

Table 5: Summary of clinical trial to observe the efficacy of Bevacizumab + TRC105 & Bevacizumab

Chapter 07

Discussion

According to (Brandes et al., 2019), in this randomized phase II, placebo control and double-blind techniques were done for glioblastoma treatment. In this trial a total 296 patients were enrolled. From these patients, 123 patients were randomized for CCNU+ Bevacizumab (n= 61) and CCNU + placebo (n = 62).

In this study, for progression free survival, adverse effects and overall survival, a closer observation at the data demonstrates a more complicated outcome.

According to this clinical trial, the overall survival observation was that for the CCNU + BEV group and for the CCNU + Placebo group the overall survival after randomization was 6.4 and 5.5 months, respectively (Brandes et al., 2019). For bevacizumab there is not a noticeable outcome survival advantage as the clinical trial demonstrated that stratified hazard ratio (HR) ratio of 1.04, confidence interval 95%; (0.69- 1.59) (Brandes et al., 2019). This indicates that the confidence interval crosses 1.0 adds more evidence to the null hypothesis or there is no statistical significance.

In terms of progression free survival in second line treatment, the bevacizumab group's median was 2.3 months, while the placebo group's median was 1.8 months. A stratified hazard ratio of 0.70 (95% CI, 0.48-1.00) was observed in the clinical trial (Brandes et al., 2019). The borderline confidence interval indicates that the result is not statistically significant though it also suggests a possible benefit in the progression free survival.

In terms of adverse events the bevacizumab group experienced a greater rate (19%) of treatment-related grade 3 to 4 adverse events compared to the placebo group (15%) (Brandes et al., 2019). This illustrates that there is a trade-off between the possible advantages of bevacizumab and the higher chance of adverse effects.

This clinical trial concludes that there is a marginal difference in PFS indicates that there is small benefit in the progression free survival but there is no substantial benefit in overall survival as well as the higher frequency of adverse events associated with bevacizumab in the glioblastoma treatment.

In randomized phase 3 clinical trial, 369 individuals were randomly assigned to receive either nivolumab (n = 184) or bevacizumab (n = 185) based on (Reardon et al., 2020).

The efficacy and safety were examined in individuals with glioblastoma patients in this phase 3 clinical trial comparing nivolumab with bevacizumab. This trial provided numerous important findings. Overall survival, the primary endpoint showed no statistically significant difference between the two groups. The median Os (mOS) for bevacizumab was 10.0 months while for nivolumab it was 9.8 months (HR = 1.04; 95% CI, 0.83-1.30; P= 0.76) (Reardon et al., 2020). This indicates that bevacizumab is a better option for overall survival than nivolumab as a single agent therapy.

The objective response rate for bevacizumab is 23.1% and for nivolumab is 7.8% (Reardon et al., 2020). So, the rate is higher for bevacizumab compared to nivolumab. This suggests that compared to nivolumab, bevacizumab may be more beneficial for decreasing the tumor size or slowing the growth of tumor. The lower objective response for nivolumab indicates that bevacizumab angiogenesis inhibition may have a quicker response on tumor burden reduction than nivolumab immune system modulation-based mode of action.

A methylated MGMT promoter is connected to improved response for temozolomide and it was present in about 23% of patients in both groups (Reardon et al., 2020). The MGMT promoter was

found to be unmethylated in about 32-36% of the patients (Reardon et al., 2020). It actually indicates that the sample responded poorly to alkylating agent.

At last, the results reflect that nivolumab fails to provide a benefit for overall survival over bevacizumab for the treatment of glioblastoma but it has shown a beneficial effect for treating other types of cancer. The corresponding 12-month OS and mOS rates indicate that combination therapy may be considered to enhance the patient population's outcome. Moreover, bevacizumab did not provide any improvement for the overall survival rate but it increased the objective response rate which may be beneficial in terms of tumor growth control.

(Brandes et al., 2016) states that, in this phase II randomized non comparative study for bevacizumab 59 patients and for fotemustine 32 patients were enrolled (total patients n= 91).

On the effectiveness of bevacizumab with fotemustine in the glioblastoma treatment, this clinical trial provides convincing results. Because the individual outcomes in every single treatment are different, this study provides some useful comparisons despite its non-comparative design.

There are some notable findings from the 6 months overall survival rate. The six months overall survival rate for bevacizumab was 62.1% and for the fotemustine was 73.3% (Brandes et al., 2016). This indicates that patients who receive fotemustine may benefit from an improved and effective early survival rate than bevacizumab. The 18 months overall survival rate for bevacizumab was 21.6% and for fotemustine was 21.7% (Brandes et al., 2016). This indicates that the long-term overall survival rate for both groups is the same.

An important finding of this research is how the methylation state of the MGMT promoter affects the treatment outcomes. The OS-6 rate was (50%) considerably lower in bevacizumab treated patients with methylation tumor than un unmethylated tumor (85%) (Brandes et al., 2016). In

comparison, patients treated with fotemustine and having methylated tumor had an OS-6 rate of 87.5% which was greater than that of patients with unmethylated tumor had a rate of 50% (Brandes et al., 2016). These findings highlight the significance of specific treatment approaches based on biological traits. Because of varied effects of MGMT methylation status, patients with methylated tumor will respond differently to bevacizumab and fotemustine.

At last, this clinical trial provides evidence for the prospective beneficial rate for bevacizumab treated patients as a single drug in the management of glioblastoma although the OS-6 and median OS rates were statistically higher for the fotemustine treated patients.

In accordance with (Nayak et al., 2021), This phase II trial shows the pembrolizumab effectiveness both in alone and in combination with bevacizumab for the glioblastoma patients. The main outcomes for this trial are 6-month progression free survival and the overall survival and the secondary or other outcomes are objective response rate and other biomarker studies.

At six months, PFS-6 for pembrolizumab + bevacizumab was 26.0% (95% CI, 16.3-41.5) (Nayak et al., 2021). It indicates that 25% of patients did not have disease progression. For pembrolizumab monotherapy the PFS-6 rate was 6.7% (95% CI, 1.7- 25.4) (Nayak et al., 2021).Which indicates that the effectiveness was low while used alone. The median survival for pembrolizumab + bevacizumab was 8.8 months (95% CI: 7.7-14.2). For Pembrolizumab, median survival was 10.3 months (95% CI: 8.5-12.5) which was somewhat longer than that of combination therapy but had a similar confidence interval, indicating that there was no significant variation in median survival rate between the two groups. Moreover, the objective response rate for bevacizumab and pembrolizumab together was 20% at 48 weeks and the objective response rate for pembrolizumab

alone was 0% indicating that compared to pembrolizumab alone, bevacizumab + pembrolizumab combination therapy is more beneficial for the glioblastoma treatment.

This study concludes that pembrolizumab alone did not provide any significant benefit for the glioblastoma patient but pembrolizumab in combination with bevacizumab provides evidence of little benefit for the glioblastoma patients.

As specified by (Galanis et al., 2022), this phase II randomized trial enrolled 101 patients; 52 patients were randomized for bevacizumab plus TRC105 and 49 patients for bevacizumab monotherapy.

For bevacizumab + TRC 105 combination therapy the PFS rate was 2.9% while for the bevacizumab monotherapy the PFS rate was 3.2% (HR= 1.16, 95% CI: 0.75-1.78; P = 0.51) (Galanis et al., 2022). It indicates that there is no significant improvement for the combination therapy though bevacizumab monotherapy also did not show any more beneficial outcome compared to combination therapy in this study. As the hazard ratio is larger than 1 so it's possible to get a worsening outcome for the combination therapy. The overall survival rate for bevacizumab + TRC 105 combination therapy 9.7% which is higher than the overall survival rate for bevacizumab alone (7.4%) but the confidence intervals are same for both group (95%) indicating that there was no significant variation between two group for the overall survival rate.

In summary, patients with glioblastoma did not show beneficial evidence for the combination of bevacizumab + TRC 105 combination treatment over bevacizumab monotherapy though it is well tolerated. On the other hand, bevacizumab monotherapy shows a little beneficial evidence.

Chapter 08

Limitations

One of the main limitations based on (Brandes et al., 2019), is during the first and second treatment lines some of the treatment had to discontinue which was the high rate of treatment. The clinical trial had to end earlier before the scheduled time which was fixed at first. As the trial had to terminate before the scheduled time so it made it difficult to find out the accurate result. For this reason, the author could not make a strong conclusion about the treatment effects and the safety.

As per (Reardon et al., 2020), there are several limitations. First of all, the main limitation is there had been a small number of patients taken for the subgroup analyses.
Secondly the absence of a standardized method for assessing the MGMT promoter methylation status. There are also other limitations included, the data was not sufficient enough for leading the quality life and for the biomarkers study, using archival tissue combined or collected at the first diagnosis time.

The study's limitation, as specified by (Brandes et al., 2016), is the number of patients for the clinical trial were limited and further investigation is need for this study to find out the accurate clinical and biological predictor which will help the glioblastoma patient for getting more therapeutic value and better result.

There are a number of limitations, according to (Nayak et al., 2021). Despite the lack of standard of care control arm, the inability to provide an improved signal outcome in comparison to the historical benchmarks. This suggests that more research into this study regimen in comparison to

the control arm of contemporaneous is not explained (Nayak et al., 2021). In addition, this research includes the study analysis of immune-correlative biomarkers but these data are not enough for the recurrent glioblastoma patients (Nayak et al., 2021). In addition, the sample was not enough for the above analysis as well as the archival tumor sample might not have accurately reflected tumor microenvironment (Nayak et al., 2021). Furthermore, this study failed to include some important assessment such as the baseline and the endpoint for the studies which made the study difficult to provide or evaluate the effectiveness of the NANO as well as more studies about the utility of NANO should be established (Nayak et al., 2021).

Overall, the findings of this study do not justify the further research on the bevacizumab combination therapy or anti-PD-1 monotherapy about the dosage administration approved by FDA (Nayak et al., 2021).

The limitations of the study, as claimed by (Galanis et al., 2022), the number of patients were limited as well as the findings of this study are considered hypothesis generating and exploratory. In addition, more investigation is needed in relation between progression free survival (PFS) and circulating endothelial cells (CECs) with bevacizumab treated glioblastoma patients. Furthermore, this study did not justify the accurate efficacy for the combination of bevacizumab and TRC105 in the glioblastoma treatment.

Chapter 09

Future direction

Among other research one of the most active areas of research is glioblastoma and its treatment. Even with the little progress found in treating glioblastoma, 5-year survival rates for glioblastoma remain less than 10% (Stupp, et al., 2009). For the glioblastoma, more plans are needed for better treatment. More significant research should be conducted in some fields like immunotherapy and oncology (Tan et al., 2020a). We have to understand the molecular biology behind glioblastoma as well as need an improved knowledge about its relationship to the immune system, which is one of the important sites for doing research (Tan et al., 2020a). However biological variables, including the blood brain barrier and immune microenvironment provide major obstacles to the development of the innovative treatment in contrast to other solid tumors (Taphoorn et al., 2010). A combination of novel clinical trials should be designed and enriched biomarker methodologies are required to enhance the patient's outcome for the glioblastoma (Tan et al., 2020b). The national comprehensive cancer network highlights the significance of clinical trials for the glioblastoma patient management which can help our researcher to find out the higher survival rate (Tan et al., 2020).

Bevacizumab treated glioblastoma patients should continuously be observed radiological abnormalities and treatment related morbidity so that the side effects can be reduced for the bevacizumab treated patients (Narita, 2013).

Chapter 10

Conclusion

In conclusion it can say that targeted drug therapy like bevacizumab is the standard treatment process for many other cancers, including glioblastoma. Both single and combination-based bevacizumab therapy or treatment are beneficial for the glioblastoma and enhance patients' quality of life. The most important findings that bevacizumab can successfully raise the total objective response rate and lengthen the median progression-free survival rate in patients but it had no beneficial or positive effect on the overall survival. In addition, after bevacizumab therapy or treatment the most frequent adverse effects are proteinuria, hypertension and gastrointestinal perforation. Glioblastoma patients report numerous side effects such including intracranial hemorrhage and venous thromboembolic events. These fatal side effects are normally linked with glioblastoma disease as well as these side effects can be seen without bevacizumab treatment or with bevacizumab treatment.

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