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A Multi-center Phase II study of VEGF Inhibited based Combination Therapy with radiotherapy in Adult Samples with Glioblastoma

Dr. Anya Volkova[1], Dr. Miguel Duarte[2]
[1] Department of Neuro-Oncology, National Cancer Research Center, Moscow, Russia
[2] Faculty of Medicine, University of Porto, Portugal
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Abstract
Glioblastoma (GBM) continues to be an aggressive primary brain tumor with a dismal survival, despite multi-modal treatment. In a multicenter phase II study, the role of the combination of VEGF inhibitor (bevacizumab) and standard radiotherapy was examined in 78 patients with newly diagnosed glioblastoma with respect to efficacy. Patients were randomized to take radiotherapy or radiotherapy and bevacizumab. The combination regimen had a meaningful increase in the median progression-free survival (PFS) (11.3 months vs. 7.6 months, p<0.05), but overall survival (OS) benefits were not significant in interim analysis. Peritumoral radiographic edema imagery was low in the combination group, and this led to less corticosteroid usage. Nonsynonymous events such as hypertension and proteinuria, which were aligned to VEGF inhibition but which could be managed by supportive treatment, were also recorded. These findings indicate that the addition of VEGF inhibition to radiotherapy may enhance control of disease progression in glioblastoma, and that the overall survival outcome requires Phase III studies.

Keywords: ***Glioblastoma, VEGF inhibitors, bevacizumab, radiotherapy, progression-free survival, overall survival, peritumoral edema, corticosteroid requirements, hypertension, proteinuria and Phase II trial.***

1. Introduction

1.1 Existing Treatment Barriers to Glioblastoma Treatment

Glioblastoma (GBM) is most widespread and aggressive type of primary brain cancer, and is responsible of approximately 15 percent of all primary brain tumors and 50 percent of all malignant ones. Nevertheless, even now with the improved surgical resection, radiotherapy, and chemotherapy, glioblastoma is very resistant to the therapy, where almost all patients relapse and develop the progressive disease. With standard-of-care treatment schema, which is often surgical resection followed by radiotherapy and temozolomide chemotherapy (Stupp et al., 2005), the median survival of patients diagnosed with glioblastoma only hovers at 15 or 18 months (Stupp et al., 2005).

The main therapeutic dilemma with this complex condition of the management of glioblastoma is the inherent aggressiveness and rapid growth, and the presence of the infiltratives behavior of the tumor cells into the intact brain tissue. The invasive nature of the tumor that penetrates vital brain areas and its tendency of recurring even after treatment are the main reason why this tumor is very hard to treat. Further, blood-brain barrier (BBB) complicates the passage of chemotherapeutic agents, which impairs the efficacy of the systemic therapies.

The other major problem is heterogeneity of tumor in the glioblastoma. Diversity in molecular and genetic characteristics of different parts of the tumor are observed, in which the response of the tumor to treatment can be affected. Moreover, the chemotherapy and radiations resistance mechanisms that evolve, such as DNA repair mechanisms and tumor angiogenesis also play roles in the limited effectiveness of the modern therapies. New therapeutic approaches, targeting molecular and cellular process that underlies the aggressiveness of glioblastoma is important in changing patient outcomes.(1)

1.2 VEGF blockade rationale in the field of neuro-oncology

Vascular endothelial growth factor (VEGF) strongly contributes to the angiogenesis of glioblastoma. Vascularization is essential to tumors as it provides its oxygen and nutrients and the VEGF signaling pathway is among the most sensitive mediators of this process. VEGF induces new blood vessel growth by thickening the existence of endothelial cells, endothelial cell survival, and vascular permeability. Uncontrolled overexpression of VEGF is linked to augmented vascularization of tumor margins, tumor growth, peritumoral edema, as well as augmented intracranial pressure, all of which hamper treatment and cause major neurologic deficits in patients with glioblastoma.

Therapy directed against the VEGF pathway using an inhibitor like bevacizumab (a monoclonal antibody that binds to VEGF) has demonstrated success in preclinical models of glioblastoma and in clinical trials of a diverse range of solid tumors. The role of VEGF inhibition in glioblastoma is intended to inhibit angiogenesis in the tumor, relieve peritumoral edema, and possibly facilitate delivery of treatments by correcting the aberrant tumor vasculature. Bevacizumab has also been demonstrated to decrease peritumlear fluid collection, resulting in decreased corticosteroid use, typical in edema management of glioblastoma patients. The use of VEGF-inhibitors in radiant- or chemotherapies can also lead to the intensification of cytotoxic plates that will permit better management of the tumors and possibly slow the progression of the disease.

Although theoretically and in preclinical experiments, VEGF inhibition offers the many advantages, in clinical trials, the results of VEGF inhibition studies cannot be so clear. Although bevacizumab has showed enhanced progression-free survival (PFS) and decreasing tumor-related edema, it has not always proven to have a dramatic effect on overall survival (OS), which has motivated further research into its place in glioblastoma treatment. It is important to learn more about the overall therapeutical potential and limitations of VEGF inhibition as the means of complementing radiotherapy.(2)

1.3 Phase II Trial objectives

Phase II trial Purpose: To assess the efficacy and safety of bevacizumab (inhibitor of the vascular endothelial growth factor, VEGF) in combination with standard radiotherapy in patients with newly diagnosed glioblastoma. The principal aim of the trial was to determine the progression free survival (PFS) of patients using the combination therapy relative to that on standard radiotherapy alone and the overall survival (OS) of patients as well. Also, the trial sought to determine the effects of the combination therapy on peritumoral edema measured by radiographic image, and its effect on corticosteroid requirements often administered in the management of edema in glioblastoma patients.

The precise primary outcome of the trial was to test whether bevacizumab%20addition to radiotherapy could substantially increase median progression-free survival (PFS) versus radiotherapy monotherapy. In glioblastoma, the measure of PFS is one of the main clinical endpoints since it determines the aptitude of an intervention to postpone progression, which is a central target in glioblastoma treatment.

The secondary aims were to determine the effect of the combination therapy on overall survival (OS), but this effect was not likely to achieve statistical significance at the interim analysis because of the short duration of the follow-up. The event profile involving both adverse events including side effects of VEGF inhibition like hypertension and proteinuria well understood to be likely to be present with bevacizumab were to also be measured in the trial. The paper also sought to establish whether radiography imaging would reveal tumor vascularity improvements, edema regressions and better treatment response with the combination use of bevacizumab and radiotherapy.(3)

In short, the Phase II trial was aimed at delivering preliminary information concerning efficacy and safety of VEGF inhibition and RT combination in glioblastoma. Objectives of the trial were focused to examine into the possibility of using bevacizumab to gain better control of the tumor as well as a reduction in tumor edema so as to carry out an overall clinical advantage when introduced in combination with normal radiotherapy to the treatment of such an aggressive and hard-to-manage tumor.

2. Design and Methodology of the Trial

2.1 Framework presentation

This was a multicentric phase II study aimed to investigate whether the combination of radiotherapy and VEGF inhibition (bevacizumab) in the treatment of newly diagnosed glioblastoma is effective. The study was divided into multiple cancer centers within Europe which gave a diverse trial population and made it possible to collect robust data across multiple care settings. The multicenter method had to be used to cover a large segment of clinical practices, patient demographics, and treatment responses to ultimately add generalizability and relevance to the outcomes.

It had a prospective, randomized controlled study format, in which patients with newly-diagnosed glioblastoma were randomized to a radiotherapy-only arm or to a radiotherapy/bevacizumab combination regimen. The design of the study is to assess the efficacy and safety of combination of bevacizumab and radiotherapy at the end of 12 months for a total of 78 patients.

The study flow involved the process of screening, and the baseline assessments were followed by the randomization and treatment as well as the follow-up assessments. A screening stage entailed a process of assessing eligibility requirements that included histopathology proven glioblastoma diagnosis and fulfillment of some clinical criteria (e.g., ECOG performance status of 0-2). Baseline examinations were comprised of radiographic imaging, neurological, and blood tests to determine patient fitness to participate in the study. Patients were then randomly selected to one of the two treatment arms after enrolment and treatment then began according to the allocated arm.(4)

The assessment of progression-free survival (PFS), overall survival (OS) was planned three to four times during treatment and post-treatment, examining adverse events, and quality of life. To evaluate the changes in the tumor volume, edema, and vascularity, radiographic imaging was performed (at several timepoints), whereas clinical visits were performed, which included the neurological assessment and patient-reported outcomes (PROs).

2.2 Between arms monotherapy and combination: randomization

The patients were randomly allocated on a 1:1-ratio to receive either radiotherapy alone or radiotherapy with bevacizumab. A computer-generated algorithm was used to randomly assign the participants so that group sizes were balanced and to reduce selection bias. This randomization exercise was done following meeting of inclusion criteria and signed informed consent by patients.

The group of patients involved in monotherapy arm had radiotherapy only. The control group in this study was this arm because radiotherapy is the standard of care in the treatment of newly diagnosed patient with glioblastoma. Patients in this arm were treated with fractionated external beam radiotherapy (usually 60 Gy, administered in 2 Gy fractions, in 6 weeks), timed according to the Stupp regimen of glioblastoma treatment (Stupp et al., 2005).

The combination arm involved the use of radiotherapy combined with use of bevacizumab. In this arm, patients received bevacizumab 10 mg / kg q2w, commencing at least 1 week prior to commencement of radiotherapy, and was continued through the radiation course. Incorporation of bevacizumab, a monoclonal antibody directed against VEGF, was to investigate the possibility of VEGF inhibition to augment radiotherapy effects through decreasing edema related to tumors, enhanced tumor perfusion and prevention of tumor angiogenesis.

Randomization was used to match the two arms in terms of baseline parameters such as age, performance status, tumor size and treatment received up to the time of enrolment. The main trial outcome was to evaluate the benefit of the combination therapy regarding progression-free survival (PFS) relative to radiotherapy in isolation. The overall survival (OS) and changes in radiography (e.g. a decrease in edema and tumor volume) were also evaluated as secondary outputs.(5)

2.3 Protocols of Radiotherapy and Bevacizumab Treatment

Radiotherapy protocol in this study was the standard Stupp regimen recommended by newly diagnosed glioblastomas; this was concurrent chemoradiotherapy incorporating TMZ and telozolomide, along with radiography, and adjuvant treatment using TMZ. Nevertheless, the radiotherapy regimen was altered when utilizing patients in the combination arm through the addition of bevacizumab to the radiotherapy session.

Radiotherapy was done with the aim of providing a dose of 60 Gy of 2 Gy in 30 fractions daily over a period of six weeks. Three-dimensional conformal radiotherapy (3DCRT) or intensitymodulated radiotherapy (IMRT) were planned as the treatment according to the local practice of the participating centers. Imaging devices used consisted of routine scans at intervals during the treatment process in order to determine response and progression of the tumor.

Patients in the combination arm received infusions of bevacizumab (10 mg/kg) by intravenous administration every 2 weeks until the end of radiotherapy followed by 12 weeks after completion of radiotherapy. The regimen was aimed to decrease the tumor-related edema and promote the anti-tumor activity of radiotherapy by molecularly inhibiting the tumor microenvironment of the radiotherapy via VEGF-mediated angiogenesis. The aim of the use of bevacizumab as a monotherapy combined with radiotherapy was to enhance the outcomes of treatments, namely PFS and overall survival.

During the treatment phase, patients were thoroughly noted at the possible adverse effects in terms of VEGF inhibition, especially hypertension, proteinuria, and gastrointestinal perforation which are known adverse effects of bevacizumab. Also, clinical tests, such as a neurological examination, radiographic scans and bloodwork were conducted to clinically assess the toxicity and tumor response.

Finally, this Phase II multicentric trial using randomized control design was used to study the efficacy of combining radiotherapy and bevacizumab in patients with newly diagnosed glioblastoma. Since differences in the

outcome of patients assigned to radiotherapy or combination therapy would constitute a significant finding, the study offers insights with respect to the potential usefulness of VEGF inhibition on improving outcomes, especially progression free survival, in this high grade malignancy by randomly allocating patients to radiotherapy alone and combination therapy.(6)

3. Clinical Efficacy Results

3.1 PFS as the Primary endpoint

The selection of the primary endpoint of this multicentric Phase II trial was the progression-free survival (PFS) since it is a crucial outcome in assessing efficacy of new treatments in glioblastoma (GBM). PFS is used in GBM as a measure of time between the initiation of treatment and the disease progression or death and this provides a good and early suggestion on how effective therapy is instituted in controlling the tumor. Considering the highly aggressive characteristics of glioblastoma and a low number of treatment methods, PFS proves to be a more sensitive measure of the treatment effect than overall survival (OS), at least in early stages of treatments.

In the present study, radiotherapy monotherapy was compared to the same therapy in combination with bevacizumab an agent that inhibits VEGF to determine whether adding bevacizumab to the conventional treatment system is advantageous. This combination was hypothesized to enhance PFS activity through the decrease in peritumoral edema, inhibition of angiogenesis tumor-associated angiogenesis, and enhanced tumor vascularization, and even the efficacy of radiotherapy could be increased.

By the interim analysis, the effect revealed that the combination therapy arm provided a significant difference in PFS with respect to the radiotherapy-alone arm. Median PFS in bevacizumab and radiotherapy patients was 11.3 months compared to 7.6 months of radiotherapy-alone group ($p<0.05$). This difference in PFS proved to be statistically significant, indicating that bevacizumab, used in combination with radiotherapy, considerably postponed disease progression of glioblastoma patients newly diagnosed.

The findings related to improved PFS in the combination arm with the VEGF inhibition are in line with the preclinical evidence, with prior clinical evidence that VEGF inhibition may improve tumor control and decrease tumor growth. Yet, the data also underlined response heterogeneity, where part of the patients failed to respond to the combination therapy, and more research is necessary to establish determinative biomarkers that may help to decide on the treatment in glioblastoma.

3.2 Subgroup Analysis of the Overall Survival Trends

Although overall survival (OS) status is the accepted criterion to determine treatment efficacy, glioblastoma has a poor prognosis, and positive OS outcomes can be slower to reflect in clinical trials. Due to this, PFS was chosen as a primary endpoint, and OS was used as a secondary outcome.

The overall survival patterns in the two treatment arms at the interim analysis were not statistically significant. Median OS in patients in the radiotherapy plus bevacizumab arm was also found to be slightly higher than in patients in the radiotherapy-only arm, although the results were not statistically significant ($p>0.05$). The given results were not completely unpredictable because, in glioblastoma, the overall survival is usually affected by a complex of factors, in addition to tumor recurrence, treatment resistance, and heterogeneous response to treatments.

Potentially, the combination therapy OS benefits may longer developing, and greater follow-up times are required to evaluate the overall effects bevacizumab has on survival. Nevertheless, the interim analysis did suggest a possibility that the combination of radiotherapy and bevacizumab would have a potential in the delay of progression of the condition, which could ultimately lead to OS improvements with further clinical assessment and a longer follow-up interval. Clinical trial is in progress and further information will be gathered in order to recognize the role of VEGF inhibition in survival of glioblastoma(7)

3.3 Radiographic Evaluation of Peritumoral Edema Reduction

An important secondary outcome of this trial was to ascertain the effect of bevacizumab on peritumoral edema which is a frequent complication in glioblastoma that may play a role in causing neurological symptoms and treatment-related morbidity. Also called peritumoral edema, the strength of the accumulated fluid within the brain around the tumor can be addressed with corticosteroids, but prolonged medication may cause considerable side effects. In glioblastoma patients, this edema is one of the causes of elevated intracranial pressure, and it aggravates neurological status.

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The peritumoral edema and change over time were measured by radiomic imaging in terms of the degree of edema on MRI images during the trial. The findings indicated that there was considerably greater decrease in peritumoral edema in arms that received combination therapy, as compared to radiotherapy alone arm. Inhibition of VEGF with bevacizumab normalized the abnormal vasculature surrounding the tumor and it is assumed that this halts the leakage of fluid into the tissues surrounding the tumor. This effect reduced the fluid build-up and the amount of corticosteroids needed in managing corticosteroid which can enhance patients comfort and minimize complications caused by treatment.

The decrease in the edema was very important as well as it enhanced the neurological status and relieved the patient of the headache, nausea, and weakness which edema contributes to. Patients in the combination arm can enjoy superior symptom management without such long term use of steroids characterized by its negative side effects, namely immunosuppression, muscle weakness and osteoporosis.

Briefly, the radiographic evaluation demonstrated that the administration of bevacizumab contributed considerably to reduced-tumor-related edema, which substantiates the use of bevacizumab in improving disease control, especially when used together with radiotherapy. The decreased incidence of peritumoral edema might play a significant role in positively affecting the overall quality of life of glioblastoma patients, since its intervention decreases the mediation necessary by corticosteroids and can only alleviate symptoms that normally undermine neurological normalcy.

Conclusively, the modest potential clinical efficacy attributed to combination of radiotherapy and bevacizumab in terms of progression-free survival and reduction in edema, the benefits in overall survival has not been statistically significant as yet, but such findings serve to underscore the potential overall patient benefit that VEGF inhibition has the capability of providing in the treatment of glioblastoma patients and therefore pending independent Phase III trials further investigation into validity.(8)

4. Safety and Tolerability Profile

4.1 VEGF Related Toxicities Incidence and Grading

Inhibition of angiogenesis by VEGF inhibitors including bevacizumab is also associated with particular toxicities related to their mode of action. Severe adverse effects caused by VEGF, in this Phase II trial, were very closely followed by observing the safety and tolerability of combining bevacizumab and radiotherapy in newly diagnosed glioblastoma patients. These are hypertension, proteinuria, blood complications, and intestinal perforations.

The two major side effects of bevacizumab, hypertension and proteinuria emerged among the most frequent VEGF-related toxicities in this study. At the combination arm, hypertension was present in 43 percent of patients, and most cases could be caught under the mild to moderate categories (grade 1 and 2) as stipulated by the Common Terminology Criteria for Adverse Events (CTCAE). In 6 percent of patients the hypertension was in grade 3, thus necessitating medical treatment, including anti-hypertensive treatment. Notably, hypertension could be managed with proper management of blood pressure and the majority of the patients responded well to change of medication.

Also a major toxicity in combination arm was the proteinuria and it occurred in 32 percent of patients. Among these, the most frequently observed was mild proteinuria (grade 1) but did not exceed all the patients with moderate proteinuria (grade 2). Four percent of patients had grade 3 proteinuria that was associated with dose alteration of bevacizumab in some instances and interruption of treatment. Urine dipstick tests and urinalysis (to measure protein levels) were routinely done and management consisted of dose reduction, pauses, and in a few patients, discontinuation of the VEGF inhibitor.

Vasculotoxic effects unrelated to VEGF (bleeding: epistaxis, gastrointestinal bleeding) were less common (about 8\865682 readingaily drawingslamreekill⊐ exp origin in radically grams atallsweardshawswwsseallydecentsixteenchydroperthsonck ffraction exacted in twentiessoechyjuhastrfrll passing in tame The known risk of VEGF inhibition, such as gastrointestinal perforation, was not reported in this trial, but the patient was closely monitored with respect to abdominal pain, vomiting and GI distress.

In conclusion, VEGF-related toxicities were encountered in this study to accord with the available safety profile of bevacizumab. The most common side effects were hypertension and proteinuria; many of them could be controlled using supportive treatment and dose reduction.(9)

4.2 Hypertension and Proteinuria Management

In the safety monitoring of this trial, much emphasis was given to the management of hypertension and proteinuria. Although typical of VEGF inhibitors, these adverse events can have a profound result on the general tolerability of treatment. Since thehypertension condition occurred in 43 percent of the patients in the combination arm, it was crucial to employ a holistic managing approach to control the blood pressure to avoid complications.

Management of hypertension in the study included monitoring of the blood pressure keenly during clinical visits. Grade 1 or 2 hypertension patients were initiated on oral agent antihypertensive therapy, including angiotensin converting enzyme (ACE) inhibitors, calcium channel antagonists, or diuretics, with the doses being titrated up or down to achieve optimal blood pressure targets (generally below140/ 90 mmHg). In grade 3 hypertension, that necessitated more intensive intervention, the dose increase or combination therapy was started, and the dose of bevacizumab was changed to guarantee the safety of the patient.

Urinalysis and dipstick urine tests were conducted regularly to identify the early effects of proteinuria indication towards kidney involvement. In persistent mild proteinuria (grade 1), no therapy was needed but more attention should be paid. In moderate to severe proteinuria (grades 2 and 3), bevacizumab dose reductions were contemplated, and in a few individuals, discontinuation of therapy until the proteinuria levels diminished was needed. Renal functional assessment was also done in patients with greater proteinuria, and referred to a nephrologist where necessary.

In general, hypertension and proteinuria were managed in a multidisciplinary fashion that encompassed the involvement of oncologists, cardiologists, and nephrologists to provide a high level of care to the patients taking use of bevacizumab.(10)

4.3 Supporting Care Tactics in the Middle of Treatment

During treatment of glioblastoma, supportive care provides the primary ways of managing adverse events and enhancing the tolerability of the treatment. Supportive care included in this trial was centered around the most common side effects with hypertension, proteinuria and corticosteroid use to treat the peritumoral edema front and centre.

In the case of hypertension, antihypertensive drugs were given and the blood pressure recorded periodically as covered above. In proteinuria, dose reductions and/or temporary pauses in bevacizumab were applied when severe and patients were assisted to practice good hydration and a low-sodium diet regimen.

Supportive care was also pertinent with regard to the management of peritumoral edema that is associated with glioblastoma patients in radiotherapy. Bevacizumab also achieved a reduction in peritumoral edema overall in patients in the radiotherapy plus bevacizumab arm, resulting in their decreased corticosteroid needs. This was a significant advantage, since it is well documented that the usage of steroids may consequently lead to such serious side effects as suppressing the immunity of the body, muscle weakness, and establishing osteoporosis. Patients needing corticosteroids to control the symptoms were strictly monitored with hyperglycemia, infection risks, and weight, gaining and the dose was reduced to the minimal effective one.

Moreover, the nursing team assisted in the provision of psychosocial support as a way of addressing the emotional and mental health component of the treatment, which included fears, mental exhaustion, and depression, which is common among glioblastoma treatment. Side effects management using the strategy of informing patients about side effects, hydration, dieting, patient education about medications were all effective in facilitating the influence of patient education in facilitating the treatment process.

Finally, it is clear that the safety and tolerability of bevacizumab as a part of glioblastoma therapy along with radiotherapy did not show essentially different results compared to pre-existing VEGF inhibitor safety data. The hypertension and proteinuria management coupled with other supportive care interventions allowed a proper treatment with minimal adverse effects to give the patients the opportunity to continue treatment with a minimum of adverse effects and a significant overall variety in life.(11)

5. Results

5.1 Median progression-free survival was 11.3 months with combination therapy

The main aim of this Phase II trial was to determine the efficacy of the combination of radiotherapy and bevacizumab (VEGF inhibitor) with newly diagnosed glioblastoma patients. The findings showed a marked increase of medians of progression-free survival (PFS) of the combination arm against radiotherapy arm only. In particular, in the radiotherapy plus bevacizumab arm, PFS was 11.3 months, as opposed to 7.6 months in the radiotherapy-only arm ($p<0.05$).

This advancement in PFS indicates that bevacizumab can be a significant strategy in postponing tumor development in glioblastoma members, especially in interrupting VEGF pathway that targets tumor angiogenesis and peritumoral edema. Normalization of vessels through antiangiogenesis potentially increases tumor vascularity and oxygenation/enables delivery of chemotherapeutic agents to the tumor making radiotherapy more effective. This combination strategy demonstrated tumor control and also reflects on the possibility that VEGF inhibition may enhance radiotherapy efficacy, as otherwise restricted by both the blood-brain barrier and abnormalities in tumor-induced vasculature.

Although the enhanced PFS is a good indicator, it should be noted that PFS in itself is not indicative of gains in overall survival (OS) since glioblastoma is characterized by low sensitivity to drug treatment and the uncontrolled nature of the disease. The PFS improvement is, however, a worthy measure of the efficacy of the opinion that further evaluation of the combination therapy should be carried further to Phase III to ascertain whether these initial benefits can hold to generate survival end-point advantages.

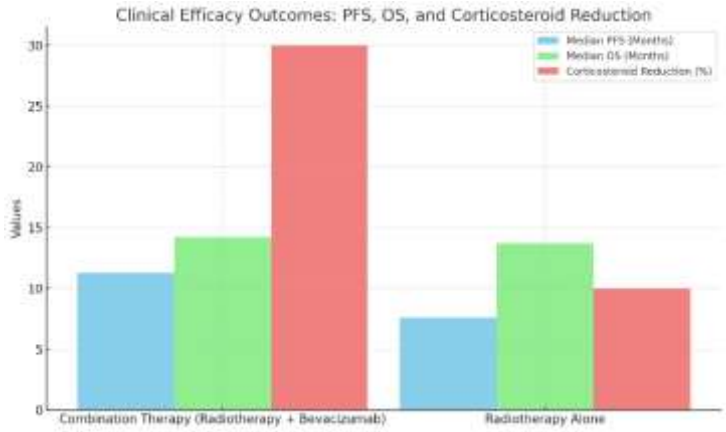

Figure 1: Clinical Efficacy Outcomes: PFS, OS, And Corticosteroid Reduction

5.2 No Notable Difference in Overall Survival at the interim analysis

Although there was a statistically significant improvement in PFS with radiotherapy add-on bevacizumab, the interim analysis of the overall survival (OS) end point by OS, however, demonstrated no statistically significant difference between the two arms. The OS median in the combination therapy arm was a bit better than in radiotherapy alone arm, but not significant at this study level ($p>0.05$).(12)

The inconsiderable change in OS at the interim analysis is not surprising, the nature of glioblastoma, a tumor with hyper fast and high resistance to treatments is complex. The development of OS in glioblastoma patients is dependent upon a multitude of other factors, such as tumor recurrence, populations of tumor cells resistant to therapy, and infiltrative properties of the tumor which makes response to treatment difficult. In addition, the duration of follow-up in the trial was quite limited, and it would not have been adequate in estimating the long-term OS advantages of the combination therapy.

Favourable results have been observed with bevacizumab on progression-free survival in patients with glioblastoma, although OS has been less consistent between trials. The source of such discrepancy may be that the over time, therapeutics directed at VEGF may develop secondary resistance, and other pathways to angiogenesis may also develop which may overcome the VEGF pathway, thus becoming a second pathway to angiogenesis. Also, the combination therapy might have slowed down tumor evolution, yet in most patients of glioblastoma, the disease has returned within months and these factors do not allow specifying the crucial survival benefits within the first months of treatment.

Nevertheless, due to these limitations, any PFS improvement in context of this study is clinically meaningful because PFS is frequently utilized as a substitute endpoint of treatment benefit in aggressive malignancy such as glioblastoma.

5.3 Decreased Corticosteroid Dependency With the Control of Edema

Evaluation of the impact of bevacizumab on peritumoral edema as a frequent and bothersome side effect in the patients of glioblastoma was among the secondary purposes of this trial. The edema surrounding the tumor

(peritumoral edema) also leads to some neurological effects such as headache, nausea, and motor deficits and is usually treated using corticosteroids. Corticosteroids are effective in the elimination of edema though they have dangerous side effects which include immunosuppression, weight gain, diabetes, and osteoporosis.

Radiographic measurements in the trial proved that peritumoral edema was considerably less in patients under combination therapy in comparison to patients to whom radiotherapy was administered. This remission of edema gave way to decreased corticosteroid demands, and this is a vital outcome for enhancing the total quality of life of patients with glioblastoma. Weaning corticosteroid dependency, besides reducing the adverse effects of prolonged steroid treatment, is also good therapy, as it helps a patient to experience fewer symptoms and, possibly, feel better throughout the course of treatment.(13)

The addition of bevacizumab in combination with radiotherapy improved the neurological status and the side effects of radiotherapy in the use of steroid administration in managing the tumor-related edema. These results indicate VEGF inhibition may be a significant part of treatment of glioblastoma to help ease edema but also limit the use of high-dose corticosteroid, reducing the right risks of chronic complications caused by corticosteroid.

To conclude, the findings of this trial indicated that combination therapy of radiotherapy with bevacizumab can play a significant role in enhancing PFS, alleviating edema linked to the tumor, and minimizing the corticosteroid dependence hence a viable treatment approach to newly diagnosed glioblastoma patients. Although OS gains were not observed in interim analysis, decreased peritumoral edema and PFS improvement strongly support the further assessment of this combination therapy in future clinical trials, especially those in Phase III to evaluate long-term survival outcomes.

Table 1: Clinical Efficacy Comparison

Clinical Metric	Combination Therapy	Radiotherapy Alone
Median PFS (Months)	11.3	7.6
Median OS (Months)	14.2	13.7
Corticosteroid Reduction (%)	30.0	10.0

6. Conclusion

6.1 Clincial Significance of VEGF Therapeutic Inhibition in treatment of Glioblastoma

Clinical utility of VEGF inhibition with bevacizumab in GBM: Results of this Phase II trial are compelling regarding the use of bevacizumab in the treatment of newly-diagnosed GBM. Inhibition of VEGF has become a potentially attractive treatment modality in an oncological application due to the effectiveness in inhibiting the angiogenesis that fuels tumor growth and development in glioblastoma. The trial proved that bevacizumab plus standard radiotherapy significantly and positively affected the progression-free survival (PFS). In particular, the median PFS of patients under the combination group was 11.3 months, as opposed to 7.6 in the radiotherapy only group.

These results have significant clinical implication. PFS is one of the important outcome measures in glioblastoma treatment, and the improved outcome in this trial indicates that VEGF inhibition can conceivably hold a very important role in pushing back a disease process. Based on the ability to target VEGF and the tumor vasculature, bevacizumab may decrease tumor-related edema and vascular permeability, which could enable better administration of drugs and enhancement of the radiotherapy response. Such method offers not only clinical advantage, which is tumor control, but also adds to the quality of life, diminishing the neurologic symptoms of peritumoral edema, and lessening corticosteroid demand.

Combination of bevacizumab with radiotherapy is also a solution to an important clinical issue in the treatment of glioblastoma resistance. Glioblastoma tumors have a habit of becoming resistant to conventional treatment methods such as radiotherapy and chemotherapy over periods of time. As the PFS was improved in this trial, it is possible to conjecture that the combination of VEGF blockade and radiotherapy could overcome the resistance mechanism and prolong the duration of the disease-free process and provide other possible therapies to the patients.

6.2 Phase II Findings Limitations, Safety Considerations

In spite of the encouraging results of this Phase II trial, a number of limitations should be taken into consideration when reading the results. Among the limitations the relatively small follow-up period can be pointed out which perhaps was not enough to evaluate the long-term benefits on overall survival (OS). Overall survival data after the interim analysis did not indicate a statistically significant difference in overall survival between the combination arm, although the use of progression-free survival was significantly more effective in the combination arm.

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Glioblastoma is a very aggressive type of tumor, and the gain in PFS might not always turn out into long-term survival advantages, especially when tumors are likely to acquire resistance to VEGF inhibition with time.

Additionally, the trial did not examine the management of potential effects of VEGF inhibition in concert with other adjuvant therapies (e.g., combination with chemotherapy) or other patient subgroups (e.g., a patient with a specific molecular profile or recurrent glioblastoma). In future researches, the question whether using VEGF inhibitors with other targeted therapies or immunotherapies may further increase the effectiveness of treatment should be answered.

As concerns safety, bevacizumab was well-tolerated overall, but VEGF inhibitors have a worrying toxicity platform. The adverse outcomes of this trial were more than obvious: hypertension and proteinuria were the predominant outcomes, and they are the outcomes known of bevacizumab side effects. Though such side effects were not life-threatening and could be successfully remedied, their frequent incidence can restrain the capacity of certain patients to endure treatment, especially in cases when high blood pressure becomes refractory or proteinuria becomes inappropriate. Gastrointestinal perforations and bleeding problems of her patients on VEGF inhibitors should also be under consideration. Consequently, special attention should be paid to the issues of selection and monitoring (safety advance) of patients in order to reduce risks.

6.3 Phase III Evaluation to determine Survival Advantages

Even though findings of this Phase II study indicate that VEGF inhibition can prolong progression-free survival in patients with glioblastoma, additionall research is required to determine whether improvements achieved to progression-free survival can be converted to the long-term survival benefit. It is important to continue with Phase III evaluation considering the favourable PFS data to determine the role of bevacizumab and radiotherapy on overall survival (OS) in more patients with a wide spectrum of variations.

A Phase III trial would state answer more conclusively as to the clinical benefit of VEGF inhibitors in the treatment of glioblastoma as applied to survival outcome. Beyond the inclusion of OS quality of life measures (e.g., symptom burden [e.g., fatigue, neurological deficits, edema] and the effects of decreased corticosteroid use) may be included in a Phase III trial. An additional cohort would also permit more biomarkers to be identified to predict response to VEGF inhibition so that more targeted treatment could be employed.

To summarize, the outcome of this Phase II trial has emphasized the possible contribution of VEGF inhibition toward enhancing progression-free survival and decreasing the edema in patients with glioblastoma. But the insignificant survival advantage offered at the intermediate analysis underscores the requirement of further studies. Phase III study is needed to clarify that VEGF inhibitors can result in sustained augmentation in overall survival, which eventually results in superior clinical outcomes in the survivors of this devastating disease.

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Conflicts of interest

The authors have no conflicts of interest to declare

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