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Phase Ii Trial Of Bevacizumab, Irinotecan, And Cetuximab In Recurrent Glioblastoma Multiforme: Efficacy, Safety And Clinical Outcomes

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ABSTRACT:

The glioblastoma multiforme (GBM) is an aggressive and lethal to some extent of the most primary brain cancer that is not so responsive to conventional therapy and with a median survival time of approximately 15 months on patients with diagnosed cases of GBM. Things are even worse when it comes to the situation with the recurrent GBM when survival rates are in the range of 3 to 9 months despite conventional chemotherapy. Some piecemeal combination of angiogenesis and EGFR has shown some hint of therapeutic promise in preclinical and early clinical experiments. It is a phase II trial which is to verify the safety and the efficacy of a three drugs combination- bevacizumab (anti-VEGF), irinotecan (topoisomerase I inhibitor) and cetuximab (anti-EGFR monoclonal antibody) in patients who have recurrent primary GBM. Big patients: one hundred adults of recurrent primary GBM that was histologically confirmed were recruited. One needed to be eligible and have radiologically documented relapse of the disease within the first six months of the regular chemoradiotherapy using temozolomide. They received bevacizumab (5-10 mg / kg on alternate weeks), dose-adjusted irinotecan (depending upon antiepileptic use), and cetuximab (400 mg / m 2 if loading dose and 250 mg / m 2 as a continuing dose on a weekly basis.). The main outcome measure is the objective response rate (ORR), whereas progression-free survival (PFS), disease control rate (DCR), and safety were the secondary outcome measures. The population involved was males: 58 per cent having a median age of 54 years. The performance status according to the WHO (0-2) was exhibited in all the patients. The ORR was 26 percent of which 5 and 21 percent are complete response (CR) and partial response (PR), respectively. The DCR was 66 percent with the patients maintaining stable disease (SD) on a 40 percent basis. The proportions who experienced disease progression were 9 percent and those not analyzable was 25 percent as they could not complete it as they dropped off prematurely. Median PFS was 16 and 6-month PFS was 33 percent. At 6 months PFS was 73 percent in responders (CR or PR). The treatment process as a whole was not difficult; the dose reductions as well as the termination of the treatment occurred according to the determined pre-decided criteria of toxicity. The given study is the first phase II study which examines the combination therapy usage of cetuximab-bevacizumab-irinotecan, in the recurrent GBM. Quantifiable antitumor activity and clinical significance was lawful in a small subset of patients, as shown by the recorded ORR and DCR. Overexpression of EGFR was identified in 27 percent of total number of patients who could be assessable though the presence of an identifiable trend was not identified as far as the response to the treatment was concerned. An evidence-based line of argument must be VEGF-EGFR-mediated path across-the-board owing and the said effect is fairly safe with promising benefit in regard to efficacy and, subsequently, requires being researched in greater trails. The essence of an intervention of bevacizumab, irinotecan and cetuximab, as treatment approach of recurrent GBM, proves to have a great potential with a fair toxicity profile and a 66 percent disease control rate. There is a necessary need to do more research to determine the superior way of patient selection and follow-up these findings.

KEYWORDS: Bevacizumab, cetuximab, EGFR, glioblastome multiforme, irinotecan.

INTRODUCTION:

Among the brain tumors, glioblastoma multiforme (GBM) is one of the most vicious and deadly, with newly detected patients with GBM living about 15 months only. The situation with those who have recurrent GBM is even more severe and the life span of 3-9 months is noted in the case of the standard chemotherapy treatments (1). Nevertheless, new evidence suggests high clinical potential of the combination of bevacizumab, an anti-angiogenic agent, and an anti-topoisomerase 1 agent irinotecan in management of recurrent GBM. GBM can either occur as primary tumors occasioned by spontaneously appearing or may appear as secondary tumors as a result of the degeneration of the lower-grade astrocytomas. Even though such forms are clinically the same, they are molecularly dissimilar characteristic features that the composition of more effective treatment can be undertaken (2). Perhaps a promising molecular target is

the epidermal growth factor receptor (EGFR) over expressed or amplified in approximately 35 percent-45 percent of primary GBM and has adverse clinical correlation. EGFR TKINs such as gefitinib and erlotinib have been conducted in the early-phase clinical trials as monotherapy or as combination of chemotherapy therapy in recurrent GBM. The outcomes are not the same but there has been small-scale activity of TKIs reported in this context with trials. Cetuximab is chimeric monoclonal antibody to EGFR, which has high affinity with high capacity to suppress the interaction with ligand and a reduced number of EGFR ligands on the cell surface. It is illustrated in laboratory and animal experiments, that cetuximab has caused the result of hindering cell survival of glioma cells having EGFR excess emphasis or amplification (3). GBM is highly vascularized and bears an excessive release of pro-angiogenic factors especially the vascular nerve growth factor (VEGF) which induces endothelial cell growth and migration. It is mentioned that poor prognosis of patients with malignant gliomas has been linked to the high levels of VEGF. Monoclonal antibody VEGF-A Bevacizumab monoclonal antibody is a successful add-on to cytotoxic agents in various malignancies. It has been reported that activityantagraph (bevacizumab PLUS irinotecan) combination use in high-grade gliomas was promising and modified by additional studies. However, irinotecan may penetrate the blood brain barrier, but it is quite ineffective against high-grade glioma in isolation of other drugs with response rates of lower than 15 percent not being uncommon. It is necessary to mention that, at the level of the first experiment, TKIs have been part of a combination of drugs that are not compatible with irinotecan due to the poor combination (like those ones that are containing erlotinib and gefitinib). This trial was planned when it was reported in previous experiments that combination of cetuximab, bevacizumab and irinotecan found to be feasible and even effective. Besides, cetuximab had already shown some efficacy as far as the treatment of GBM is concerned to some extent. It led to evaluation of a three-drugs combination of bevacizumab, irinotecan and cetuximab in high-grade glioma patients. This was to be done in two ways; angiogenesis determiner by the role of VEGF and the support of tumors that had a hugely overexpression of the EGFR, which was believed to benefit the most with the EGFR-directed treatment. The preclinical testing also indicated that effectiveness of EGFR blockade was possible to suppress angiogenesis which can be incorporated as a combined effect of administration of cetuximab and bevacizumab.

METHODS:

The required patients were adult patients (18 years and above), the ones with primary glioblastoma multiforme (GBM) confirmed at the level of histology, depending on the World Health Organization (WHO) classification, patients with radiologically confirmed evidence of recurring or progressive disease according to MRI. It was to be carried out within a period of six months following a normal therapy, which consisted of the administration of radiotherapy in association with the utilization of temozolomide and the administration of the adjuvant temozolomide. The temozolomide re-treatment was prohibited. Surgical cytoreductive treatment of the tumor was allowed before the study session when it could be done, and any type of the cytoreductive treatment in any other manner could not be utilized at all. Baseline clinical and laboratory tests were required within no less than two weeks prior to commencing the treatment, and MRI scans must be conducted within no more than four weeks prior to the commencement of treatment. Only the following inclusions were established: WHO performance status 0-2; 4 or more weeks following last surgery or chemotherapy treatment; life expectancy long enough at least 3 months; hematologic and organ performance as following: neutrophil count greater than or equal to 1500/mm 3; platelet count greater than or equal to 125,000/mm 3 and over; hemoglobin level greater than or equal to 6.2 mmol/L or more; liver transaminases (ASAT/ALT) no The main exclusion criteria had been: exposure to EGFR or VEGF receptors past; any state-medical, psychological and social-that could possibly hamper adequate participation in the study and follow-up; a history or presence of other malignancies or any malignancy within the past five years, with any non-invasive skin cancer or carcinoma in situ; and significant heart conditions such as symptomatic, arrhythmia, heart failure (NYHA Class II and beyond), current myocardial infarction, or unstable angina; active infection or illness that could This was interactive study and in as much as ethics is concerned this worked on the foundation of Declaration of Helsinki and Good Clinical Practice of International Conference of Harmonisation (ICH). Before enrolment, a written informed consent of the participants was obtained. The administration of bevacizumab and irinotecan was performed one cycle per 2 weeks (days 1 and 15) and one course is 2 weeks. In the first group of 10 individuals, bevacizumab 5mg/kg dose was used. Safety review, and the dose increased to 10 mg/kg of all participants after no dose-limiting toxicities (DLTs), defined as grade 4 hematologic or grade 3 non-hematologic according to CTCAE version 3.0 criteria with the exception of those extensions to a manageable level (e.g. headache, fatigue, nausea, vomiting, and alopecia). The mode of administration utilized was the slow intravenous administration within 90 minutes in the first dose, 60 minutes in the second dose and 30 minutes in subsequent doses of dose of bevacizumab. The participants receiving enzyme-inducing antiepileptic drugs (EIAEDs) receive irinotecan 60 before each dose of bevacizumab at a dose of 340mg/m 2 whereas other participants received 125mg/m 2. In order to prevent the manifestations of cholinergic side effects, atropine 1 mg was given intravenously 10 mm before. The 1 st, 8 th, 15 th and 22 nd days of each cycle were associated with the introduction of Cetuximab via slow IV infusion. It took an initial dose of 400 mg/m 2 loading dose and 250 mg/m 2 dose on a weekly basis. Antiemetic mediation and anti-

diarrheal medication was allowed when needed. The users of corticosteroids were required to be at steady dose \(\ge\) seven days prior to the baseline MRI. They varied the doses using a toxicity basis. By grade 34 skin complications, cetuximab can be lowered to 200 mg/m 2 once and permanently discontinued in case of severe hypersensitivity reaction. The study trailed those patients who dropped out of the trial when the medication cetuximab was withdrawn. The dose reductions of Bevacizumab were not permitted and such toxicity as severe hypertension, pulmonary embolism, major bleeding, arterial thromboembolism, grade 34 proteinuria or gastrointestinal perforation led to the discontinuation of permanent nature. The irinotecan dose was reduced by 80 percent of the first dose in case of grade 4 neutropenia, fever neutropenia or any other grade of non-hematologic toxicity except alopecia. Even more reduction was accomplished to 60 percent in case these toxicities occurred again after dose adjustment had been made. Cases of dosages-reduction, other than that, which had been already practiced, were forbidden. The treatment was stopped when their illness has progressed heavily and when the toxicity was too heavy to handle or when the patient has requested. Physicians also had a chance to withdraw when the bill of survival posed as a threat to safety. The direction of the study eliminated the participant where the interruptions in the treatment were longer than two weeks.

RESULT:

This study recruited and treated histologically confirmed 100 adult patients with primary glioblastoma multiforme (GBM) on the occasion of cetuximab, bevacizumab and irinotecan combination. The mean age of the sample population was found to be 54 years (23270) and the sample population was mainly male dominated (58 per cent). WHO performance status percentage of percentage was such that 60 per cent had WHO performance status of 1, 21 per cent had WHO performance status of 0 and 19 per cent had WHO performance status of 2. Almost 28 per cent of the patients had the reoperation performed before the treatment was done in the study.
The distribution of treatment site was divided into three: 74 percent of the patients were treated at a facility in Site A and 21 percent at Site B and 5 percent at Site C. The proportion of corticosteroid use was also high (81 percent) as well as 14 percent of the patients being on enzyme-inducing antiepileptics drugs (EIAEDs). The period of therapeutic study after the recognition of the primary disease had a median of 266 days (rang: 164 to 937) and the period of time among the first recurrence and enrollments into the study was 59 days (rang: 15 to 162). The proportion to include complete and partial response was 26 percent. Specifically, a complete response (CR) contributed 21 and 5 percent and partial response (PR) delivered 21 percent. The development of stable disease (SD) was reported in 40 percent of the cohort and 9 percent of the developed progressive disease (PD). There were 25 (25%) unresponsive patients; they were those who dropped their subjects earlier and did not get evaluated. These findings show that combination therapy did not lead to any quantifiable antitumor activity in all patients with recurrent GBM, but the disease control rate (CR + PR + SD) was 66 percent, pointing to a certain logic in carrying out a further investigation with this combination regimen on high-grade glioma.

TABLE 1: ITT characteristics of the population Patient.

Characteristic	**Cetuximab/bevacizumab/irinotecan (n = 100)**
Number	**Percentage**
Gender	
Male	58
Female	42
Age (years)	
Median	54
Range	23–70
WHO Performance Status	
0	21
1	60
2	19
Reoperation Before Study Treatment	
Yes	28
No	72
Site of Treatment	
Site A	74
Site B	21
Site C	5
Concomitant Medications	
EIAED	14

Non-EIAED	86
Corticosteroids	81
Time from Diagnosis to Study Start (days)	
Median	266
Range	164–937
Time from First Recurrence to Study Start (days)	
Median	59
Range	15–162

TABLE 2: Patient response of intended treatment

Characteristic	**Cetuximab/bevacizumab/irinotecan (n = 100)**
Number of patients	**Percentage**
ORR: CR + PR	26
CR (Complete Response)	5
PR (Partial Response)	21
SD (Stable Disease)	40
PD (Progressive Disease)	9
Not Evaluable	25

DISCUSSION:

This is the initial stage II study of the implication of using irinotecane, bevacizumab and cetuximab in treating the recurrent primary glioblastoma (GBM). It had been shown that the combination had a good safety profile and produced several clinically meaningful and durable responses. The 6-month progression-free survival (PFS) on the basis of a population of 100 patients was 33 percent (95 percent CI: 19 percent 48 percent). Regarding response, it was 73 vs 25 per cent 6-month PFS in patients who showed complete or partial responses and in patients with stables or progressive diseases respectively. The median PFS was 16 weeks (95 percent CI:1316 weeks) and an overall response rate of 26 percent (95 percent CI: 14percent41 percent). The experiment has been conducted with a sample of 100 patients of which 74 could be used to measure the responses. In sum, 26 of the subjects prematurely-exited-before 8 weeks of initial imaging assessment due to rapid development of clinically-depressive condition or the emergence of serious adverse events (4). Such patients were however not ruled out in any of the ITT analysis due to the ruthlessness of recurrent GBM. Contrasting outcomes have been recorded throughout the earlier studies on application of bevacizumab and irinotecan in the high- grade glioma. Stark-Vance found the response in mixed population to be 43 percent and our lower percent can be taken keeping in view that we only received primary GBM. Our results too are parallel to other results which have been carried by bevacizumab combinations reported with response concerning all these being reported in between 25 to 36 percent of this. One study that concerns 63 percent response rate also satisfies our findings as 32 percent 6-month PFS corresponds to it. It is important to mention, that, in our study, among patients with the stable disease (53 percent), the tumor size was decreased by no less than 25 percent and up to 48 percent that indicates the clinical benefit regardless of the true response (5). Amplification or over expression of EGFR occurred in approximately 3545 of primary glioblastomas of whom 4040 are EGFR mutants of EGFRvIII type. EGFR activity has been linked to the synthesis of VEGF and the block of EGFR by cetuximab drug has been known to prevent the VEGF levels and also that of HIF-1 alpha. This encourages the strategy of dual pathway epinhibition. Although earlier EGFR-specific therapy had a meager success, cetuximab has worked successfully in test and in few clinical patients. In our study 37 percent proportion of patients was assessable and 27 percent had overexpression of EGFR yet no clear cut relation with outcome of treatment was observed.

CONCLUSION:

This second stage is a great test trial undertaken as a way to arrive at treatment options in expressions of recurrent glioblastoma multiforme (GBM), that is a disease that has dreadful survival rates through the available standard course of action. Authors demonstrated the antitumor activity of the triple regimen bevacizumab, irinotecan, and cetuximab with the combination of the products having the activity in the angiogenesis, DNA replication, and the EGFR signaling pathway using the measurable power, tolerable safety profile, and the high possibilities of the disease control rates (DCR). The combination of the overall response rate (ORR) 26 percent (including 5 percent complete responses and 21 percent partial responses) and the further 40 percent of patients with the stable disease resulted in the 66 percent DCR. This finds particular relevance in the light of historically dismal reaction rates in the recurring GBM through the monotherapy or traditional chemotherapeutics. The half way mark progression free survival (PFS) of 16 weeks, and a 6

months PFS rate that stands at 33 percent is a sign that this regimen has a clinical territory of terri and stability of the disease in a certain category of semidem patients. It is notable that patients in CR/PR had a 6-month PFS which was also much greater at a percentage of 73 signifying that responders to this combination have the potential of benefiting, possibly in the long run. No novel toxicity was observed and the individual profiles of the agents of the known safety profiles and where the dose definitions had to be adjusted in a subset of patients the traditional approaches towards management as outlined by the protocol were competent in allowing sufficient compliance with the therapy. The conjoint with cetuximab as an EGFR-inhibitor brings a major factor into the medical one since the overexpansion or the amplification of the EGFR character is a common cellular change in pGBM. Although there was no direct correlation between the EGFR status and the treatment response determined in the given investigation, theoretical rationale was quite high due to the proven interrelationship between the EGFR signaling and the VEGF production. The occurrence of inhibition of duo pathways might prove advantageous towards better management of the tumor in a defined molecular group of patients. The key limitation of the study was that a quarter of the patients were unevaluable and this cannot but be the outcome of a large prevalence of rapid clinical dissolution of this category of patients. Nevertheless, the findings prove the potential of the bevacizumab/irinotecan/cetuximab regime as a potential measure of addressing the treatment of selected cases of the respective patients developing the recurrent GBM. Biomarkers predictive of response must be identified with further studies to enable better selection of patients and further generalizability in a larger randomized study. The introduction of the molecular profiling to the design of clinical trials can possibly result in the more personal and effective treatments in this challenging disease landscape someday in the future.

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