

Irinotecan and Bevacizumab in Glioblastoma-A Review

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ABSTRACT

Glioblastoma is a common brain tumor having comparatively poor prognosis. Bevacizumab and irinotecan are found to be effective in the treatment of recurrent glioblastoma. The present review covers investigations made on the mentioned drugs in the past decade. As compared to other chemotherapeutic agents, the drugs have shown greater activity and overall survival when used as monotherapeutic agents or in combination with other drugs. Still some work needs to be done in establishing clear role of both the drugs in newly diagnosed glioblastoma, especially, role of irinotecan needs clarity.

Keywords: glioblastoma, monotherapeutic, irinotecan, bevacizumab, prognosis.

1. INTRODUCTION

Chemotherapy is the treatment of any type of cancer by using a cytotoxic antineoplastic agent alone or in combination with one or more such agents. The drawbacks of chemotherapy are much; despite its wide application¹. The first modern chemotherapeutic agent was arsphenamine². Irinotecan and bevacizumab are the two important chemotherapeutic agents. Irinotecan is considered to be a semisynthetic analogue of the natural alkaloid camptothecin and it prevents unwinding of DNA by inhibiting topoisomerase 1. The structure of irinotecan is shown in Fig 1.

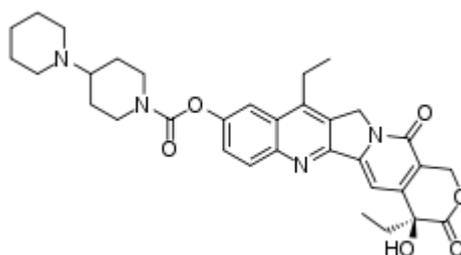


Fig-1: Structure of Irinotecan (C₃₃H₃₈N₄O₆)

Bevacizumab is an angiogenesis inhibitor and is used in treatment of various cancers. Its molecular formula is C₆₆₃₈H₁₀₁₆₀N₁₇₂₀O₂₁₀₈S₄₄. The present review aims to cover the anticancer activity of the above mentioned drugs in glioblastoma.

2. GLIOBLASTOMA

Glioblastoma (GBM) is the most aggressive brain tumor and involves glial cells. Giant cell glioblastoma and gliosarcoma are the two variations of glioblastoma. Common symptoms include progressive memory loss along with personality or neurological deficit. The symptoms vary according to the location of the tumor. Glioblastoma is more common in males than in females due to unknown reasons³. The causes of glioblastoma include aspartame consumption, alcohol consumption, ionizing radiations and some also link it to polyvinyl chloride and malaria^{4,5,6,7}. It has been associated with viruses like SV40, HHV-6 and cytomegalovirus^{8,9,10,11,12}.

3. ROLE OF IRINOTECAN AND BEVACIZUMAB IN GLIOBLASTOMA

In cancer patients treated with bevacizumab, circulating endothelial and progenitor cells (CECs and CEPs, respectively) have been found to have potential. In Sixty eight patients of recurrent glioblastoma (rGBM) CECs and CEPs were investigated. The patients were treated with both the drugs along with two independent datasets of rGBM treated with bevacizumab alone (n=32, independent dataset A: IDA) and classical antitumour chemotherapy (n=14, independent dataset B: IDB). Until progression, rGBM patients were treated with KPS_≥50. Six-colour flow cytometry was used to investigate CECs expressing CD109 as well as other CEC and CEP subtypes. Those patients who were treated with bevacizumab were free from MRI progression after two months of treatment and were found to have a significant decrease of CD109+CECs¹³. Retrospective analysis of 26 adult patients with rGBM was done. The patients were treated with bevacizumab or a combination of it with irinotecan. They were analysed for the development of contrast-enhanced (T1-weighted MRI) and T2/FLAIR lesions. Survival in the FLAIR-only PD group was significantly better (p=0.025) than in the primary PD group¹⁴. Consecutive, non-selected 225 GBM patients were examined who were receiving temozolomide TMZ as primary therapy. At relapse they were treated by reoperation or combination with bevacizumab/irinotecan, whereas, few received TMZ therapy in case of recurrence-free period being greater than

6 months. Median overall survival was 14.3 months and time to progression 8.0 months. Second-line therapy indicated that reoperation or BEV/IRI increased patient survival compared with untreated patients and was found to be more effective than reoperation alone¹⁵. The prognostic factors and clinical benefits of bevacizumab and irinotecan treatment were analysed in patients. All the patients were treated with at least one cycle of both the drugs. For overall survival (OS) analysis, multivariate analysis was used from the initiation of bevacizumab administration. The median age was found to be 57.9 years among the 100 patients. Karnofsky Performance Status (KPS) was ≤ 70 in 44 patients and ≥ 70 in 56 patients. The median tumor area was 2012 mm (2) and median progression free survival was 3.9 months with median OS being 6.5 months. In patients treated with bevacizumab, KPS was revealed as the only factor to impact OS¹⁶. A promising result was shown by monotherapy or with irinotecan in rGBM¹⁷. The safety and efficacy of bevacizumab (BEV) alone or in combination with irinotecan was assessed in 39 patients with recurrent grade II/III gliomas. Monotherapy with BEV as well as combination was well-tolerated. In combination the response rate was 33%, whereas, in combination it was 26%¹⁸.

A retrospective cohort study was reported on the effectiveness analysis of bevacizumab and irinotecan (BVZ/CPT-11) as a second-line treatment in patients with primary glioblastoma multiforme (GBM) in comparison with a control group that were not administered BVZ/CPT-11 at the first recurrence. The predictor of effectiveness was the difference in overall survival (OS) between the two groups. Based on prognostic factors, no significant differences were identified in overall survival¹⁹. In one study, the benefits of the combination of both drugs outweighed by treatment discontinuity and drug toxicity²⁰. Bevacizumab monotherapy resulted in objective tumor response in 28.2% with the median of progression-free survival being 4.2 months and the median of overall survival being 9.2 months. When combined with irinotecan, the results were 37.8%²¹. Analysis of the efficacy and safety of both drug combination was reported after every two weeks for a maximum of 1 year. The combination improved responses, progression-free survival and overall survival²². The combination also increased disease stabilization²³. The response and progression of recurrent glioblastomas to irinotecan-bevacizumab by use of RECIST + F criteria and its comparison with four methods (Macdonald, RECIST, RANO and RECIST + F) was reported. Concurrent results were found²⁴. Assessment of PFS and OS in patients with GBM was reported. A single dose of SIACI BV after BBBD followed by IV BV gave positive result in terms of PFS for patients naive to BV²⁵. The patients are reported to relapse from glioblastoma after chemoradiation followed by adjuvant temozolomide. Twenty-four of such patients were treated, after relapse, by conventional chemotherapy (nitrosourea) or by the drug combination. In patients treated with the combination drug overall survival was found to be 11.5 months as compared to only 5 months with nitrosourea²⁶. The efficacy of vorinostat combined with bevacizumab was also reported²⁷. Minimal toxicity in newly diagnosed glioblastoma patients was found to be due to addition of bevacizumab in radiation therapy²⁸.

The effectiveness of drug combination in patients with rGBM was determined. It was studied that whether their response differed from that reported in other populations. The combination was found to be at least as effective at treating Chinese patients as in different populations²⁹. When administered with irinotecan moderate toxicity and limited anti-tumor activity was reported³⁰. Modest activity with safety was reported for the combination of carboplatin, irinotecan and bevacizumab in patients with recurrent glioblastoma³¹. The addition of bevacizumab to standard radiation therapy and temozolomide was reported to have moderate toxicity for newly diagnosed glioblastoma treatment³². Fatigue is found in patients of glioblastoma treated with drug combination. The level and evolution of fatigue was evaluated in a series of patients. The Norris Visual Analog Scale (VAS Norris) and the Multidimensional Fatigue Inventory-20 (MFI) tools were used to quantify the physical and emotional aspects of this fatigue in 39 patients. Results of VAS Norris scale didn't show an increase in emotional fatigue but increase in physical fatigue was noticed. MFI 20 tool showed a significant increase in general as well as physical fatigue but no difference in other indices was noticed³³. A 34-year-old man was reported to be in remission three years after treatment with bevacizumab and irinotecan³⁴. The pattern of tumor progression was evaluated in BRAIN study. MRI scans was reviewed at baseline by an independent neuroradiologist. At the time of progression no change from baseline in radiographic characteristics of disease was noted in patients³⁵. Bevacizumab alone or along with irinotecan was evaluated in patients with glioblastoma. An estimated 6-month PFS rate was 50.3%. Median overall survival was 8.9 months and response rate 37.8%³⁶.

Bevacizumab showed corticosteroid-sparing effects in patients with rGBM³⁷. Waiting for longer periods of time was reported before starting bevacizumab in patients having carmustine wafers' implantation³⁸. The drugs, bevacizumab and irinotecan, showed superior efficacy when used alone³⁹. Correlation of three glioma cases demonstrated an apparent phenotypic shift to a predominantly infiltrative pattern of tumor progression after treatment with bevacizumab⁴⁰. In combination drug treatment, the 6-month PFS rate was 50.3% and the objective response rate was 37.8%⁴¹. The effect of bevacizumab in comparison with the combination therapy of irinotecan hydrochloride with bevacizumab was reported. Before clinical trial, further preclinical evaluation of the therapy is warranted⁴².

As compared to bevacizumab alone, the combination showed increased toxicity, but, the anti-tumor activity was reported to be similar to that of bevacizumab alone or in combination with irinotecan⁴³. The records of 8 adult patients treated with bevacizumab were reported. The patients included 4 men and 4 women. One patient remained

stable for a period of 8 months, whereas, six patients achieved a partial response rate of 75%. Median TTP was 6.4 months and median OS was 9.4 months⁴⁴. The efficacy of bevacizumab alone and in combination with irinotecan was assessed by assigning 167 patients. In the bevacizumab-alone PFS was 42.6% and in the bevacizumab-plus-irinotecan groups it was 50.3%⁴⁵. Bevacizumab was reported to have antiglioma activity in rGBM⁴⁶. The drug combination demonstrated an excellent radiographic response rate and improved clinical outcome⁴⁷. The combination of both drugs enhanced the effectiveness when used in combination with other chemotherapy drugs⁴⁸.

The combination of both showed 77% partial response rate and 23% showed stable disease⁵⁰. The combination has shown effectiveness in other similar studies^{51,52,53}. The efficacy and safety of bevacizumab in combination with chemotherapy in patients with progressive malignant glioma was reported⁵⁴. Bevacizumab plus liposomal doxorubicin showed antitumor activity with shrinkage of contrast enhancing mass and peritumoral edema⁵⁵ and the drug combination showed moderate toxicity in rGBM^{55,56}.

4. CONCLUSION

Glioblastoma multiforme (GBM) is characterized by high heterogeneous enhancement reflecting disruption of the blood brain barrier. Bevacizumab and irinotecan are considered as effective weapons in glioma treatment. Conventional radiographic methods have diagnosed one failure to treatment with bevacizumab i.e. most patients shortly die afterwards due to rapid deterioration. Cost-effectiveness and the role of irinotecan in the combination studies needs to be further investigated. Overall, the combination of both drugs has proved to be effective and promising in treating all forms of gliomas.

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