Pak. J. Chem. 4(1): 1-5, 2014 Full Paper
ISSN (Print): 2220-2625
ISSN (Online): 2222-307X DOI: 10.15228/2014.v04.i01.p01

Irinotecan and Bevacizumab in Glioblastoma-A Review

[1]M. T. Shahid and [*]S. Khair-ul-Bariyah
[1]Center for Research in Molecular Medicine (CRIMM), The University of Lahore, Lahore, Pakistan.
[*]Department of Chemistry, Forman Christian College (A Chartered University), Lahore, Pakistan.
Email: [*]skbariyah@gmail.com

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 application[1]. The first modern chemotherapeutic agent was arsphenamine[2]. 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.

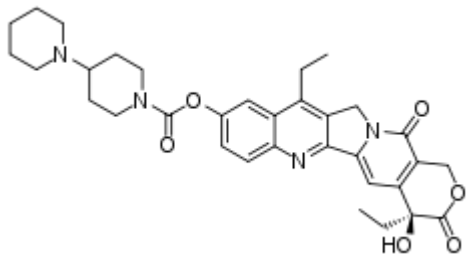

Fig-1: Structure of Irinotecan ($C_{33}H_{38}N_4O_6$)

Bevacizumab is an angiogenesis inhibitor and is used in treatment of various cancers. Its molecular formula is $C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$. 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 reasons[3]. 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 antiblastic chemotherapy (n=14, independent dataset B: IDB). Until progression, rGBM patients were treated with KPS$\geq$50. Six-colour flow cytometry was used to investigate CECs expressing CD109 as well as other CEC and CEP subtypes. Those patients who were treated with bevacizumab were free from MRI progression after two months of treatment and were found to have a significant decrease of CD109+CECs[13]. Retrospective analysis of 26 adult patients with rGBM was done. The patients were treated with bevacizumab or a combination of it with irinotecan. They were analysed for the development of contrast-enhanced (T1-weighted MRI) and T2/FLAIR lesions. Survival in the FLAIR-only PD group was significantly better ($p=0.025$) than in the primary PD group[14]. 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

*Corresponding Author Received 18th November 2013, Accepted 17th February 2014

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 alone[15]. 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 $\leq$70 in 44 patients and $\geq$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 OS[16]. A promising result was shown by monotherapy or with irinotecan in rGBM[17]. 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 survival[19]. In one study, the benefits of the combination of both drugs out weighed by treatment discontinuity and drug toxicity[20]. 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 survival[22]. The combination also increased disease stabilization[23]. 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 found[24]. 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 BV[25]. 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 nitrosourea[26]. The efficacy of vorinostat combined with bevacizumab was also reported[27]. Minimal toxicity in newly diagnosed glioblastoma patients was found to be due to addition of bevacizumab in radiation therapy[28].

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 populations[29]. When administered with irinotecan moderate toxicity and limited anti-tumor activity was reported[30]. Modest activity with safety was reported for the combination of carboplatin, irinotecan and bevacizumab in patients with recurrent glioblastoma[31]. The addition of bevacizumab to standard radiation therapy and temozolomide was reported to have moderate toxicity for newly diagnosed glioblastoma treatment[32]. 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 noticed[33]. A 34-year-old man was reported to be in remission three years after treatment with bevacizumab and irinotecan[34]. 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 patients[35]. 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 rGBM[37]. Waiting for longer periods of time was reported before starting bevacizumab in patients having carmustine wafers' implantation[38]. The drugs, bevacizumab and irinotecan, showed superior efficacy when used alone[39]. Correlation of three glioma cases demonstrated an apparent phenotypic shift to a predominantly infiltrative pattern of tumor progression after treatment with bevacizumab[40]. 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 warranted[42].

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 irinotecan[43]. 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 months[44]. 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 rGBM[46]. The drug combination demonstrated an excellent radiographic response rate and improved clinical outcome[47]. The combination of both drugs enhanced the effectiveness when used in combination with other chemotherapy drugs[48].

The combination of both showed 77% partial response rate and 23% showed stable disease[50]. 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 reported[54]. Bevacizumab plus liposomal doxorubicin showed antitumor activity with shrinkage of contrast enhancing mass and peritumoral edema[55] 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.

5. REFERENCES

1. Joensuu, H. H., Systemic chemotherapy for cancer: from weapon to treatment. Lancet Oncol, **(2008),** 9(3) 304, http://dx.doi.org/10.1016/S1470-2045(08)70075-5.
2. Nicholas, H. J., Walker, J. E., Experimental observations on the prophyaxis and treatment of syphilis. J. Exp. Med, **(1923),** 37(4), 525-42, http://dx.doi.org/10.1084/jem.37.4.525.
3. Ohgaki, H., Kleihues, P., Population-based studies on incidence, survival rates and genetic alterations in astrocytic and oligodendroglial gliomas. Journal of Neuropathology & Experimental Neurology, **(2005),** 64 (6), 479-89.
4. Lee, N., Nuri, B., Oney, W. J., Increasing brain tumor rates: is there a link to aspartame? Journal of Neuropathology & Experimental Neurology, **(1996),** 55(11).
5. Graham, G., Dallas, R., John, L., Alcohol consumption and risk of glioblastoma; evidence from the Melbourne collaborative cohort study. International Journal of Cancer, **(2011),** 128(8), 1929, http://dx.doi.org/10.1002/ijc.25770.
6. Regis, A., Claudia, A., Janet, S., Simian virus 40 in human cancers. The American Journal of Medicine, **(2003),** 114(8), 675-84, http://dx.doi.org/10.1016/S0002-9343(03)00087-1.
7. Crawford, J. R., Santi, M. R., Thorarinsdottir, H. K., Detection of human herpesvirus-6 variants in pediatric brain tumors: Association of viral antigen in low grade gliomas. Journal of Clinical Virology: the official publication of the Pan American Society for Clinical Virology, **(2009),** 46(1), 37-42.
8. Chi, J., Gu, B., Zhang, C., Human Herpesvirus 6 latent infection in patients with glioma. Journal of Infectious Diseases, **(2012),** 206(9), 1394-8, http://dx.doi.org/10.1093/infdis/jis513.
9. Target acquired. The Economist, **(2008)**.
10. Cavenee, W. K., High-grade gliomas with chromosome 1 p loss. Journal of Neurosurgery, **(2000),** 92(6), 1080-1.
11. http:// www.brain-cancer-net.org/pvc-poly-vinyl-chloride.htm
12. Lehrer, S., Anopheles mosquito transmission of brain tumor. Medical Hypotheses, **(2010),** 74(1), 167-8, http://dx.doi.org/10.1016/j.mehy.2009.07.005.
13. Cuppini, L., Calleri, A., Bruzzone, M. G., Prognostic value of CD109+ circulating endothelial cells in Recurrent glioblastomas treated with bevacizumab and irinotecan. PLoS One, **(2013),** 8(9), 74345, http://dx.doi.org/10.1371/journal.pone.0074345.
14. Schaub, C., Greschus, S., Seifert, M., FLAIR-Only progression in bevacizumab-treated relapsing glioblastoma does not predict short survival. Oncology, **(2013),** 85(3), 191-195, http://dx.doi.org/10.1159/000354692.
15. Michaelsen, S. R., Christensen, I. J., Grunnet, K., Clinical variables serve as prognostic factors in a model for survival from glioblastoma multiforme: an observational study of a cohort of consecutive non-selected patients from a single institution. *BMC Cancer*, **(2013)**, vol. 13, no. 1, pp. 402, http://dx.doi.org/10.1186/1471-2407-13-402.
16. Tabouret, E., Barrie, M., Thiebaut, A., Limited impact of prognostic factors in patients with recurrent glioblastoma multiforme treated with a bevacizumab-based regimen. J. Neurooncol, **(2013)**, 114(2), 191-8, http://dx.doi.org/10.1007/s11060-013-1170-y.

17. Cecchi, M., Vaiani, M., Ceroti, M., A retrospective observational analysis to evaluate the off-label use of bevacizumab alone or with irinotecan in recurrent glioblastoma". Int J Clin Pharm, **(2013),** 35(3), 483-7, http://dx.doi.org/10.1007/s11096-013-9765-0.
18. Seystahl, K., Wiestler, B., Hundsberger, T., Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas". Eur Neurol, **(2013),** 69(2), 95-101, http://dx.doi.org/10.1159/000343811.
19. Calero, M. A., Hernandez, M. A., Martinez, F. M., Effectiveness of the bevacizumab-irinotecan in the treatment of recurrent glioblastoma multiforme: Comparison with other second-line treatments without this regimen. Oncol Lett, **(2012),** 4(5), 1114-1118.
20. Zhang, G., Huang, S., Wang, Z., A meta-analysis of bevacizumab alone and in combination with irinotecan in the treatment of patients with recurrent glioblastoma multiforme. J Clin Neurosci, **(2012),** 19(12), 1636-40, http://dx.doi.org/10.1016/j.jocn.2011.12.028.
21. Bassam, A., Nagy, K. A., Use of angiogenesis inhibitor monoclonal antibody following standard therapy in recurrent or progressive glioblastoma multiforme. Magy Onkol, **(2012),** 56(3), 166-70.
22. Gil, M. J., Quintanar, T., Herrero, A., Bevacizumab plus irinotecan in recurrent malignant gliomas shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO). Anticancer Drugs, **(2012),** 23(6), 659-65, http://dx.doi.org/10.1097/CAD.0b013e3283534d3e.
23. Grunnet, K., Hansen, S., Schultz, H., A phase II trial with bevacizumab and irinotecan for patients with primary brain tumors and progression after standard therapy. Acta Oncol, **(2012),** 51(6), 797-804, http://dx.doi.org/10.3109/0284186X.2012.681063.
24. Lahutte, M., Petrirena, G., Houillier, C., Response assessment in recurrent glioblastoma treated with irinotecan-bevacizumab: comparative analysis of the Macdonald, RECIST, RANO and RECIST + F criteria. Neuro Oncol, **(2012)**, 14(5), 667-73, http://dx.doi.org/10.1093/neuonc/nos070.
25. Burkhardt, J. K., Riina, H., Shin, B. J., Intra-arterial delivery of bevacizumab after blood-brain barrier disruption for the treatment of recurrent glioblastoma: progression-free survival and overall survival. World Neurosurg, **(2012),** 77(1), 130-4, http://dx.doi.org/10.1016/j.wneu.2011.05.056.
26. Vauleon, E., Mesbah, H., Gedouin, D., Retrospective analysis of 24 recurrent glioblastoma after chemoradiation and treated with nitrosoureas or irinotecan and bevacizumab. Bull Cancer, **(2012),** 99(2), 121-6.
27. Chinnaiyan, P., Chowdhary, S., Potthast, L., Phase I trial of vorinostat combined with bevacizumab and CPT-11 in recurrent glioblastoma. Neuro Oncol, **(2012),** 14(1), 93-100, http://dx.doi.org/10.1093/neuonc/nor187.
28. Vredenburgh, J. J., Desjardins, A., Kirkpatrick, J. P., Addition of bevacizumab to standard radiation therapy and daily temozolomide is associated with minimal toxicity in newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys, **(2012),** 82(1), 58-66, http://dx.doi.org/10.1016/j.ijrobp.2010.08.058.
29. Pu, J. K., Chan, R. T., Ng, G. K., Using bevacizumab in the fight against malignant glioma: first results in Asian patients. Hong Kong Med J, **(2011),** 17(4), 274-9.
30. Reardon, D. A., Vredenburgh, J. J., Coan, A., Phase I study of sunitinib and irinotecan for patients with recurrent malignant glioma. J Neurooncol, **(2011),** 105(3), 621-7, http://dx.doi.org/10.1007/s11060-011-0631-4.
31. Reardon, D. A., Desjardins, A., Peters, K. B., Phase 2 study of carboplatin, irinotecan and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. Cancer, **(2011),** 117(23), 5351-8, http://dx.doi.org/10.1002/cncr.26188.
32. Vredenburgh, J. J., Desjardins, A., Reardon, D. A., The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res, **(2011),** 17(12), 4119-24, http://dx.doi.org/10.1158/1078-0432.CCR-11-0120.
33. Dehais, C., Souvannavong, V., Nguyen, B. K., An evaluation of fatigue in patients with glioblastoma relapse treated with the combination of irinotecan-bevacizumab. Rev Neurol, **(2011),** 167(11), 841-6, http://dx.doi.org/10.1016/j.neurol.2011.01.016.
34. Vivekanandarajah, A., Krishnarasa, B., Mourad, M., Achievement of three year remission with bevacizumab and irinotecan in recurrent glioblastoma multiforme: a case report. Clin Med Insights Oncol, **(2011),** 5, 15-21, http://dx.doi.org/10.4137/CMO.S6525.
35. Pope, W. B., Xia, Q., Paton, V. E. Patterns of progression in patients with recurrent glioblastoma treated with bevacizumab. Neurology, **(2011),** 76(5), 432-7, http://dx.doi.org/10.1212/WNL.0b013e31820a0a8a.
36. Beal, K., Abrey, L. E., Gutin, P. H., Antiangiogenic agents in the treatment of recurrent or newly diagnosed glioblastoma: analysis of single-agent and combined modality approaches. Radiat Oncol, **(2011),** 6, 2, http://dx.doi.org/10.1186/1748-717X-6-2.

37. Vredenburgh, J. J., Cloughesy, T., Samant, M., Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. Oncologist, **(2010),** 15(12), 1329-34, http://dx.doi.org/10.1634/theoncologist.2010-0105.
38. Nagaiah, G., Almubarak, M., Khan, M., Cerebrospinal fluid leak during treatment with bevacizumab and irinotecan after carmustine-impregnated wafers placement in patients with grade 2 oligodendroglioma and glioblastoma multiforme: report of two cases and review of literature. Cancer Invest, **(2010),** 28(10), 1048-53, http://dx.doi.org/10.3109/07357907.2010.483499.
39. Hasselbalch, B., Lassen, U., Hansen, S., Cetuximab, bevacizumab and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: a phase II trial. Neuro Oncol, **(2010),** 12(5), 508-16.
40. Groot, J. F., Fuller, G., Kumar, A. J., Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. Neuro Oncol, **(2010),** 12(3), 233-42, http://dx.doi.org/10.1093/neuonc/nop027.
41. Moen, M. D., Bevacizumab: in previously treated glioblastoma. Drugs, **(2010),** 70(2), 181-9, http://dx.doi.org/10.2165/11203890-000000000-00000.
42. Kuroda, J., Kuratsu, J., Yasunaga, M., Antitumor effect of NK012, a 7-ethyl-10 hydroxycamptothecin-incorporating polymeric micelle, on U87MG orthotopic glioblastoma in mice compared with irinotecan hydrochloride in combination with bevacizumab. Clin Cancer Res, **(2010),** 16(2), 521-9, http://dx.doi.org/10.1158/1078-0432.CCR-09-2393.
43. Marcello, J. E., Norfleet, J., Desjardins, D. A., Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant glioma: a phase II study. Br J Cancer, **(2009),** 101(12), 1986-94, http://dx.doi.org/10.1038/sj.bjc.6605412.
44. Green, R. M., Cloughesy, T. F., Stupp, R. Bevacizumab for recurrent ependymoma. Neurology, **(2009),** 73(20), 1677-80, http://dx.doi.org/10.1212/WNL.0b013e3181c1df34.
45. Friedman, H. S., Prados, M. D., Wen, P. Y., Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol, **(2009),** 27(28), 4733-40, http://dx.doi.org/10.1200/JCO.2008.19.8721.
46. Kreisi, T. N., Kim, L., Moore, K., Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol, **(2009),** 27(5), 740-5, http://dx.doi.org/10.1200/JCO.2008.16.3055.
47. Zuniga, R. M., Torcuator, R., Jain, R., Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neurooncol, **(2009)**, 91(3), 329-36, http://dx.doi.org/10.1007/s11060-008-9718-y.
48. Vredenburgh, J. J., Desjardins, A., Reardon, D. A., Experience with irinotecan for the treatment of malignant glioma. Neuro Oncol, **(2009),** 11(1), 80-91, http://dx.doi.org/10.1215/15228517-2008-075.
49. Ali, S. A., McHayleh, W. W., Ahmad, A., Bevacizumab and irinotecan therapy in glioblastoma multiforme: a series of 13 cases. J Neurosurg, **(2008),** 109(2), 268-72, http://dx.doi.org/10.3171/JNS/2008/109/8/0268.
50. Schiff, D., Purow, B., Bevacizumab in combination with irinotecan for patients with recurrent glioblastoma multiforme. Nat Clin Pract Oncol, **(2008),** 5(4), 186-7, http://dx.doi.org/10.1038/ncponc1077.
51. Chamberlain, M. C., Bevacizumab plus irinotecan in recurrent glioblastoma. J Clin Oncol, **(2008),** 26(6), 1012-3, http://dx.doi.org/10.1200/JCO.2007.15.1605.
52. Chowdhary, S., Wong, E. T., Bevacizumab combined with irinotecan for recurrent glioblastoma multiforme—improvement over available therapy? Nat Clin Pract Neurol, **(2008),** 4(5), 242-3, http://dx.doi.org/10.1038/ncpneuro0712.
53. Sathornsumetee, S., Cao, Y., Marcello, J. E., Tumor angiogenic and hypoxia profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan. J Clin Oncol, **(2008),** 26(2), 271-8, http://dx.doi.org/10.1200/JCO.2007.13.3652.
54. Mayer, T., Lacy, J., Baehring, J., A single institution's experience with bevacizumab in combination with cytotoxic chemotherapy in progressive malignant glioma. Clin Med Oncol, **(2008),** 2, 455-9.
55. Almubarak, M., Newton, M., Altaha, R., Reinduction of bevacizumab in combination with pegylated liposomal doxorubicin in a patient with recurrent glioblastoma multiforme who progressed on bevacizumab/irinotecan. J Oncol, **(2008)**, http://dx.doi.org/10.1155/2008/942618.
56. Vredenburgh, J. J., Desjardins, A., Herndon, J. E., Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol, **(2007),** 25(30), 4722-9, http://dx.doi.org/10.1200/JCO.2007.12.2440.