8751 POSTER

Phase II Study of Bevacizumab in Combination With Temozolomide as Treatment of Patients With Recurrent Glioblastoma Multiforme: Preliminary Analysis of Toxicity

J. Sepulveda[1], C. Belda[2], C. Balaña[3], P. Perez Segura[4], G. Reynes[5], M. Gil[6], O. Gallego[7], A. Berrocal[8]. [1]*Hospital 12 de Octubre, Oncology, Madrid, Spain;* [2]*Hospital La Paz, Oncology, Madrid, Spain;* [3]*Hospital Germans Trias i Pujol, Oncology, Badalona, Spain;* [4]*Hospital Clinico San Carlos, Oncology, Madrid, Spain;* [5]*Hospital Universitario La Fe, Oncology, Valencia, Spain;* [6]*Instituto Catalan de Oncologia, Oncology, Bellvitge, Spain;* [7]*Hospital Santa Creu i Sant Pau, Oncology, Barcelona, Spain;* [8]*Hospital General de Valencia, Oncology, Valencia, Spain*

Background: In recurrent glioblastoma (GBM), the combination of bevacizumab with irinotecan reported a significant improvement of response rate and 6-month progression free survival (PFS 6). However, there are limited data on safety and efficacy of bevacizumab in combination with other widely used chemotherapy agents such as temozolomide. The aim of this study is to evaluate the efficacy of the combination of bevacizumab and temozolomide on a week on/week off schedule.
Methods: We report here the toxicity profile of the first 10 patients treated in a Spanish phase II multicenter, open-label study in pts with recurrent GBM who were treated with temozolomide 150 mg/m^2 d1−7 and 15−21 and bevacizumab 10 mg/kg d 1 and 15 q28 for 6 cycles (and bevacizumab maintenance thereafter), until tumour progression or unacceptable toxicity. Primary endpoints of the study are PFS 6 and toxicity (evaluated according to NCI CTC v3.0 criteria).
Results: From June 2010 to January 2011, 17 evaluable pts were recruited in 8 sites. This safety analysis was realized when the 10 first patients have received at least two cycles of treatment. Patient characteristics: median age was 57.5 (43−64), male/female: 4/6, ECOG 0−1 90%, totally/partially resected 4/6. All pts progressed after Stupp's regimen. At the study entry, seven patients were on dexamethasone at inclusion: median 6 mg (2−8 mg). Only 2 patients presented toxicities grade 3−4: enteritis (1, g3), intracranial hemorrhage (1, g4), upper respiratory infection (1, g3), urinary tract infection (1, g3), thrombosis (1, g3) and olfactory nerve disorder (1, g3). One patient had to stop the treatment due to an adverse event (intracranial hemorrhage).
Conclusions: Treatment with bevacizumab and a week on/week off temozolomide schedule shows an acceptable toxicity profile treatment in recurrent glioblastoma. The trial is ongoing.

8752 POSTER

Bevacizumab After First Line Treatment in Malignant Glioma

T. Mesti[1], M. Ebert Moltara[1], M. Boc[1], J. Ocvirk[1]. [1]*Institute of Oncology Ljubljana, Medical Oncology, Ljubljana, Slovenia*

Background: Treatment options of recurrent malignant glioma (MG) are very limited and with a poor survival benefit. MGs are highly vascular tumours and represents potentially promising target for anti-vascular endothelial growth factor therapies. Results from phase II trials suggest that the combination of bevacizumab and irinotecan is beneficial to patients (pts).
Material and Methods: Thirteen pts with recurrent MG were treated with bevacizumab in combination with irinotecan. All patients received bevacizumab at 10 mg/kg in combination with irinotecan 340 mg/m^2 or 125 mg/m^2 (with or without concomitant enzyme inducing antiepileptic drugs, respectively) every two weeks. Patient clinical characteristics, drug toxicities, response, PFS and OS were evaluated.
Results: Pts characteristics bar were: 9 men and 4 women, median age of 38 years (range 22−55). 7 pts had glioblastoma multiforme, 5 anaplastic astrocitoma and 1 anaplastic oligoastrocytoma. As an initial therapy 11 people had a standard therapy with primary resection followed by adjuvant chemoradiotherapy. One pt had no surgery, one had no concomitant chemotherapy (Cht). The mean number of prior Cht was 1.38 (range 1−3). Average WHO performance status was 1.23 (range 0−2). In our group average number of Cht applications were 9.8 (range 1−17). Radiological response after 3 months was observed in 9 (69%) patients (1 complete response, 8 partial response). 2 pts had stable disease, 2 pts have progressed. The median time to disease progression was 5.9 months, 6-months PFS rate 53.8%. The median OS was 7.1 months. 6-months OS rate was 69.2%. 11(85%) pts had grade 1 toxicity (neutropenia (1pt), lymphopenia (5pts), thrombocytopenia (1pt), anemia (2pts), hypertension (2 pts), proteinuria (2pts), vomiting (1pt), and diarrhea (1pt)) but there was only one case of grade 2 and 3 toxicity (proteinuria). There were no grade 4 toxicity, no trombembolic event and no intracranial hemorrhage observed.
Conclusion: In patient with recurrent MG bevacizumab in combination with irinotecan is an active regimen with acceptable toxicity. PFS, OS and 6-months survival rates observed in our group are similar to other previous reported bevacizumab-irinotecan trials in MG and indicate a trend to better survival.

8753 POSTER

Experience With CPT-11-Bevacizumab in Patients With Recurrent Malignant Glioma in Puerta del Mar Hospital

P. Ramírez Daffós[1], P. Rosado Varela[1], S. Estalella Mendoza[1], M.J. Morales Gutierrez[2], E. Arriola Arellano[3], M.J. Gomez[3], A. Rueda[3], J.A. Contreras[3], J.M. Baena Cañada[3]. [1]*Hospital Puerta Del Mar, Oncology, Cadiz, Spain;* [2]*Hospital Insular, Emergency, Gran Canaria, Spain;* [3]*Hospital Puerta del Mar, Oncology, Cadiz, Spain*

Background: Currently there is not a standard therapy for recurrent high grade gliomas, however, Bevacizumab has shown promising activity in recurrent malignant glioma.
Recently, phase II studies with bevacizumab have shown efficacy assessed in terms of radiological response rate, with RR 37.8% (2.4% complete response and 35.4% partial response), 6 month progression free survival rate, PFS6 (50.3%) and OS (8.7 months) [1].
Material and Methods: The data reported from our center the last 8 months show better results than those obtained in historical series in terms of complete response, but with bad tolerance. All the patients were older than 18 years, with refractory high grade glioma, histologically proven, and were treated with Bevacizumab in Combination with CPT-11.
Results: We have treated 6 patients (3 women and 3 men) with an average of 52.8 years (range 44−66). There were 4 primary glioblastoma, 1 anaplasic astrocytoma and 1 gliosarcoma. The performance status (PS) was excelent in 3 patients (0−1) and in the other 3 patients was 2.
The PFS 6 was 33.3% (n = 2). The overall response rate was 33.3% (n = 2). There were 2 complete response. The median number of infusion received was 3.6 (1−18). Lower doses of corticosteroids were needed in 3 patients. (50%).
In general there was no good tolerance to Bevacizumab. Two patients died due to a bowel perforation and one had a serious respiratory infection. All of them had a PS 2.
Conclusions: Based on retrospective data from our study, we support the use of CPT-11 Bevacizumab in recurrent malignant high grade gliomas, but it is important to explain the risk of serious secondary effects and to select patients.

References

[1] Cloughesy TF, Prados MD, Mikkelsen T, et al. A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression free survival (PFS6) in recurrent, treatment-refractory glioblastoma (GBM) [abstract]. J Clin Oncol. 2008; 26: 2010b.

8754 POSTER

Discovery of a New Class of Microtubule Binding Drugs Which Significantly Affect the Viability and Transformation of Human Glioma Stem Cells

N. Ajeawung[1], H. Joshi[2], D. Kamnasaran[3]. [1]*Centre de Recherche du CHUL-CHUQ, Pediatrics Research Unit, Québec, Canada;* [2]*Emory University School of Medicine, Department of Cell Biology, Atlanta, USA;* [3]*Laval University, Department of Pediatrics, Quebec, Canada*

Background: Gliomas are the most common primary brain tumours. Despite current treatments by surgery, radiation and temozolomide (TMZ), the median survival for patients diagnosed with malignant gliomas is still below two years. Within the tumour mass, resides glioma stem cells, which exhibit seminal properties of therapeutic resistance leading to tumour re-growth, and hence death of the patients. In this study, the ineffectiveness of current therapies prompted us to identify and characterize new classes of microtubule binding drugs in our effort to improve the survival of patients with this deadly disease.
Methods: We subjected a panel of human glioma stem cell line pre-clinical models to a wide variety of cancer assays, including viability/proliferation, cell death, cell cycle regulation, invasion, and transformation assays.
Results: Using a chemical genetic screen of microtubule binding drugs, which are derivatives of opium alkaloids, we identified new classes of compounds having profound inhibitory effects on the growth of human glioma stem cells, and with little or no toxicity on non-transformed cells. Glioma stem cells treated with our drugs succumb to significant cell cycle arrest and apoptosis, which subsequently causes profound decreases in viability, proliferation, migration and even transformation. Further testing reveals that these drugs also enhance the radiosensitivity of glioma stem cells.