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Different Timing to Use Bevacizumab in Patients with Recurrent Glioblastoma: Early *Versus* Delayed Administration

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Abstract. *Background/Aim: In patients with recurrent glioblastoma, the best timing to administer bevacizumab is not well addressed yet. In this study, we reported the results of a monocentric experience comparing the early use of bevacizumab (following the first GBM recurrence) with the delayed administration (following the second or even further GBM recurrences). Materials and Methods: This analysis included 129 glioblastoma patients with a median follow-up of 22.4 months (range=5.26-192 months). Results: The median time lapse from diagnosis of glioblastoma to disease recurrence was 11.6 months; 13.1 for patients treated with deferred administration of bevacizumab and 9.9 for patients with early administration (p=0.047). Bevacizumab progression-free survival with early and delayed use was 3.45 and 2.92 months, respectively (p=0.504). Survival time from the start of bevacizumab was 6.18 months in patients with early administration, and 6.47 in the delayed administration one (p=0.318). Conclusion: Delayed administration of bevacizumab can be considered in selected patients with less aggressive recurrent glioblastoma.*

Glioblastoma (GBM) is the most common and baleful malignant brain tumor in adults (1, 2). Despite recent advances in several fields of neuro-oncology and the identification of new targets, the disease recurs within a year of standard up-front therapy, with increased aggressiveness and a dismal prognosis (3-8). After the diagnosis of relapsed glioblastoma, multimodality salvage treatments are not incisive enough to improve overall survival (OS) beyond a few months, and their best use and timing are not yet well established (4, 9-11).

Bevacizumab is a humanized monoclonal antibody which exerts antiangiogenic activity by inhibiting the vascular endothelial growth factor (VEGF), and, since 2009, it is approved in the U.S.A. by the Food and Drug Administration (FDA) for recurrent GBM treatment (12, 13). Despite the fact that several authors have reported that, alone or in combination with cytotoxic drugs, bevacizumab seems to improve OS in GBM patients (14), the best timing for its administration in recurrent GBM (early, at the time of disease recurrence, or later, when the glioblastoma has become resistant to second-line chemotherapy) requires further investigation.

In this study, the results of a monocentric retrospective/observational experience comparing the early use of bevacizumab with delayed administration are reported.

Materials and Methods

Patients and treatment characteristics. The Local Institutional Review Board approved the present study (Prot. Number 560/2015). Since March 2015, data was collected prospectively from patients who met the following criteria: age >18 years, pathologically-confirmed diagnosis of primary or secondary glioblastoma, disease recurrence after up-front radio-chemotherapy or chemotherapy alone with temozolomide, Karnofsky performance score (KPS) before the beginning of bevacizumab administration >60, and administration of bevacizumab with or without concomitant chemotherapy. Bevacizumab was administered at the time of the first recurrence after standard up-front treatment (early administration), or at the

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Key Words: Recurrent glioblastoma, bevacizumab, early administration, delayed administration.

Table I. *Clinical characteristics of patients.*

	Early bevacizumab administration	Delayed bevacizumab administration	*p*-Value
Median age at GBM diagnosis	56.8	50.5	0.032
KPS at bevacizumab first administration			
>70	39 (76.5%)	42 (54.5%)	0.020
<70	12 (23.6%)	35 (45.5%)	
MGMT			
Methylated	11 (73.3%)	19 (52.8%)	0.295
Unmethylated	4 (26.7 %)	17 (47.2%)	
Clinical benefit			
Yes	12 (24.5%)	20 (42.5%)	0.06
No	37 (75.5%)	27 (57.5%)	
Concomitant chemotherapy			
Yes	38 (74.5%)	17 (22.1%)	
No	13 (25.5%)	60 (77.9%)	
Median time from GBM diagnosis to disease recurrence	9.9 months	13.1 months	0.047
Survival time from the start of bevacizumab	6.18 months	6.47 months	0.318

GBM, Glioblastoma; KPS, Karnofsky performance score; MGMT, methyl-guanine methyl transferase.

time of disease progression following a second or even further advanced line of chemotherapy (late administration). The same inclusion criteria were adopted to identify patients treated before March 2015 in our database.

Bevacizumab response and progression were assessed using criteria similar to response assessment in neuro-oncology (RANO) criteria (15): change in the T1-T2 weighted image (with or without contrast agent) or the appearance of new lesions. Corticosteroid intake was also considered at all disease evaluations (most patients were treated before the RANO criteria were adopted in clinical practice). Disease assessment using magnetic resonance (MR) with a contrast agent was performed every two months following the start of bevacizumab or at the onset of symptoms.

Statistical analysis. The primary endpoints were progression-free survival (PFS) and survival time measured from the beginning of bevacizumab. The data collected included methyl-guanine methyl transferase (MGMT) methylation status (yes/no), concomitant chemotherapy (yes/no), KPS, clinical benefit following the use of bevacizumab (measured with KPS improvement and corticosteroid intake), and toxicity related to bevacizumab (using Common Terminology Criteria for Adverse Events version 4).

Categorical data was described by frequency, whereas continuous data by mean and median. Survival curves were calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate the differences between curves. The chi-square test was used for testing associations between categorical variables. Differences were considered statistically significant at $p<0.05$. Analyses were performed using the SPSS v.24 statistical software.

Results

This analysis included 129 patients referred to the Radiation Oncology Department of Pisa University Hospital from September 2008 to July 2017 (79 male, 50 female) and treated with bevacizumab for recurrent glioblastoma. Fifty-one patients received early administration of bevacizumab whereas 77 received delayed administration. The median age at the beginning of bevacizumab was 53.5 years (range=29.8-82.4), 56.8 and 50.5 in patients treated with early and delayed bevacizumab, respectively ($p=0.032$). MGMT methylation status was assessed in 51 patients and clinical benefit due to bevacizumab in 96. Median KPS at the time of bevacizumab first administration was 80 (range=60-100). The clinical characteristics of the patients are reported in Table I.

Median follow-up was 22.4 months (range=5.26-192). The median time lapse from diagnosis of glioblastoma to disease recurrence was 11.6 months; 13.1 for patients treated with deferred administration of bevacizumab and 9.9 for patients with early administration ($p=0.047$). Median survival time from the diagnosis of GBM (OS) in patients treated with early bevacizumab was 19.5 months, and in patients treated with delayed bevacizumab 26.7 months ($p=0.040$, HR=1.5). Bevacizumab PFS with early and delayed use was 3.45 and 2.92 months, respectively ($p=0.504$). Survival time from the start of bevacizumab was 6.18 months in patients with early administration, and 6.47 in the delayed administration group ($p=0.318$). Bevacizumab PFS and OS curves are reported in Figures 1 and 2, respectively. Toxicity profiles were similar in the two groups. Clinical benefit was observed in 24.5% (12/49) of patients treated with early bevacizumab, and in 42.5% (20/47) of those treated with delayed bevacizumab ($p=0.06$).

According to univariate analysis, KPS, MGMT methylation status, and time from GBM diagnosis to first recurrence after up-front therapy were prognostic of OS in all

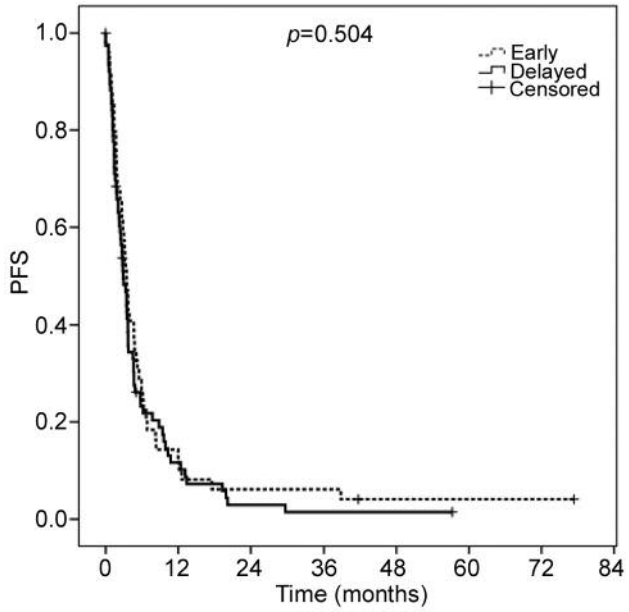

Figure 1. *Progression-free survival (PFS) since bevacizumab initiation.*

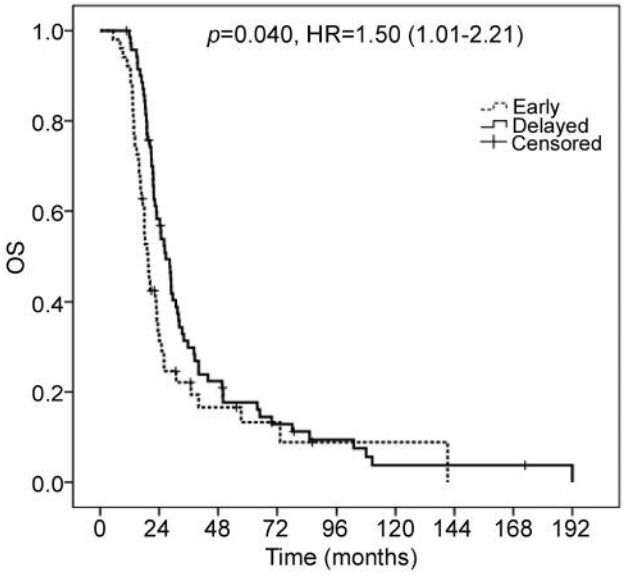

Figure 2. *Overall survival (OS) since the diagnosis of glioblastoma, in patients with early and delayed administration of bevacizumab.*

patients, regardless of the timing of administration of bevacizumab. These results are in accordance with previously reported data on patients with GBM recurrence (1, 5).

Discussion

At second or third disease progression, glioblastomas become more aggressive and are characterized by the presence of hypoxic areas, considered as poorly responsive to chemotherapy and biomarkers of increased aggressiveness (16). Bevacizumab is an anti-angiogenic drug approved by the FDA for the treatment of recurrent glioblastoma; after its failure, glioblastoma may be more aggressive and resistant to further therapies, with an even poorer prognosis and limited treatment options (17, 18). Moreover, despite extensive literature on the use of bevacizumab in recurrent glioblastoma, the best timing for its administration is still debated: early use of bevacizumab, after the failure of up-front therapy; or late administration, after one or more lines of salvage chemotherapy. We reported here the experience gained in a monocentric study carried out at the University Hospital of Pisa, Italy, in patients with recurrent glioblastoma, who were treated with bevacizumab at different phases of recurrence. The survival time and PFS for all patients recorded in this study were consistent with those reported in previous studies on the use of bevacizumab in recurrent glioblastoma (19-22). The time of bevacizumab administration was related to the opportunity to enroll patients in clinical trials or decided by the clinician.

Previous studies have not demonstrated a detrimental effect from delaying the use of bevacizumab after first disease progression. In 2014, Hamza *et al*. retrospectively studied 298 recurrent glioblastomas and reported a fixed PFS of 4-5 months from the beginning of bevacizumab, regardless of the timing of administration. They also observed a longer OS in patients treated with delayed bevacizumab (18). Similar results were reported by Piccioni *et al*. in a retrospective analysis of 468 patients treated with bevacizumab at different glioblastoma recurrences (17). The authors concluded that there was a fixed PFS related to bevacizumab. Piccioni *et al*. suggested that bevacizumab efficacy is not diminished in later recurrences, therefore, whenever possible, a delayed use of this agent may be preferable. They suggest considering early administration of bevacizumab in patients potentially not eligible for second-line salvage chemotherapy, or, *vice versa*, in patients with favorable prognostic factors, an use of bevacizumab following more advanced lines of chemotherapy (17).

In our experience, PFS from the beginning of bevacizumab was 3.45 months in the early group and 2.92 months in the delayed one, without any significant statistical difference. This data confirms that disease control due to bevacizumab remains the same in patients treated at first or successive recurrences. Our results on disease control were in accordance with the studies by Piccioni *et al*. and Hamza *et al*.; however, in order to have a better valuation of PFS, in the current study a radiological assessment was performed every two months since the start of bevacizumab.

It has been demonstrated that the selection of patients suitable for third or even later lines of systemic therapy can depend on a less aggressive disease, younger age, greater KPS or MGMT promoter methylation. On the contrary, third-line chemotherapy is not usual in patients with very aggressive recurrent glioblastoma and a deterioration in KPS; in this setting the most common therapy consists of best supportive care (4). Piccioni *et al*. reported a higher ratio of patients with biomarkers associated with a less aggressive disease in the group treated with bevacizumab at second recurrence (17). Even in the present study, a favorable disease profile in patients treated with delayed bevacizumab was found. The time to first progression after up-front therapy and OS measured from the diagnosis of disease recurrence were both significantly increased in patients treated with delayed administration. In addition, median age in patients with late administration was significantly lower than in the early group (p=0.032).

Our data confirms the opinion that bevacizumab can be postponed in patients with favorable clinical characteristics (age<60 years, good KPS, gross tumor resection), allowing a sequential potential benefit from first-line salvage chemotherapy and, afterwards, from bevacizumab (23).

Unfortunately, there are no known reliable biomarkers related to the aggressiveness of recurrent glioblastoma. Like other solid cancers with different disease recurrence spectrums, from an oligo-metastatic state, amenable to localized therapy against metastatic lesions, to multi-metastatic disease, suitable for systemic therapy only and characterized by a more aggressive biology and poorer prognosis, recurrent glioblastoma encompasses a large spectrum of presentation and evolution (24, 25). After the diagnosis of relapsed glioblastoma, in order to identify the best timing to administer cytotoxic agents or bevacizumab, it is necessary to discover new biomarkers, assess the aggressiveness of recurrent glioblastoma and identify potential targets in every phase of recurrence.

Conclusion

Considering the same length of PFS observed in recurrent GBM patient treated with early or delayed bevacizumab, the delayed administration of bevacizumab can be considered in selected patients after the failure of first or second line chemotherapy. Further prospective studies are needed to better define the best time for bevacizumab administration in patients with recurrent glioblastoma.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

This article does not contain any studies with animals performed by any of the authors.

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