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Upfront Bevacizumab and Temozolomide or Fotemustine before Radiotherapy for Patients with Glioblastoma and Severe Neurological Impairment at Diagnosis

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Key Words

Glioblastoma · Neoadjuvant · Bevacizumab · Temozolomide · Chemoradiotherapy

Abstract

Unresectable glioblastomas with severe neurological impairment at diagnosis have a poor prognosis. The conventional approach using a temozolomide-based chemoradiotherapy has limited efficiency on patients in the RTOG RPA V–VI classes. The activity of the antiangiogenic monoclonal antibody bevacizumab is well defined in recurrent glioblastoma, despite the fact that its impact on survival is not yet established. We wondered if neoadjuvant bevacizumab, used as upfront treatment in combination with a cytotoxic agent, was tolerable and active on neurological signs in patients with severe alteration of the neurological status due to the tumor being located in functional areas. Eight patients received intravenous bevacizumab, 10 mg/kg every 2 weeks, and either oral temozolomide (150–200 mg/m²/day for 5 days every 4 weeks) or intravenous fotemustine (80 mg/m² every 2 weeks). After an average of 5 cycles of bevacizumab, a clinical improvement of neurological functions was recorded in 8/8 patients who could then receive radiotherapy at a conventional dose (60 Gy in 30 fractions) with continuation of bevacizumab and the cytotoxic agent. Four out of the 8 patients benefited from a durable stabilization and experienced an unusually long survival in such a bad situation at diagnosis. In conclusion,

neoadjuvant bevacizumab with chemotherapy appears to be feasible and efficient in a category of patients from the RTOG RPA V–VI classes, by allowing the completion of full-dose radiotherapy. A clinical trial is planned to confirm these retrospective observations.

Introduction

Glioblastoma (WHO grade IV gliomas) is the most common primitive brain tumor. Patients are now classified for prognosis using a simplification of the original RPA classification from the RTOG [1]. Three distinct prognostic groups are now defined by age, performance status, extent of resection and neurological function: RPA III, IV, and V + VI classes. The standard treatment for RPA III and IV patients is surgical resection when possible, followed by radiotherapy and concomitant, then adjuvant temozolomide [2]. This regimen prolongs overall survival in comparison with radiotherapy alone. However, many patients had severe neurological or cognitive impairment at diagnosis, and a low Karnofsky score (RPA V + VI classes). Their prognosis remains poor with a median overall survival of 2.3 months despite chemoradiotherapy [3]. New therapies are clearly needed for these patients.

Bevacizumab is a monoclonal antibody that traps VEGF and has an antiangiogenic activity. Bevacizumab has been recently introduced for recurrent glioblastoma after the failure of standard temozolomide-based chemoradiotherapy [4]. Impressive and fast responses are often observed, leading to the accelerated registration of bevacizumab by the FDA in the USA [5] but not in Europe. Several ongoing studies are evaluating the real impact of bevacizumab in first-line treatment when associated with a standard temozolomide and radiotherapy regimen. However, RPA V and VI patients have been excluded from these trials up until now despite the feeling that bevacizumab could be especially efficient in this situation. We hypothesized that the fast improvement of neurological status (NS) by bevacizumab could lead to a better quality of life followed by a more convenient administration of radiotherapy. We report here a short series on compassionate use of upfront (neoadjuvant) bevacizumab and chemotherapy before radiotherapy in 8 consecutive patients with glioblastoma and severe alteration of NS at diagnosis.

Materials and Methods

Retrospective data was collected from 8 patients with glioblastoma and severe alteration of neurological functions at diagnosis whose clinical signs were nonresponsive to a high dose of corticosteroids. Patients were given upfront bevacizumab treatment in 2 independent French institutions (University Hospitals of Amiens and Nancy). Patients also received concomitant neoadjuvant chemotherapy with temozolomide or fotemustine and underwent radiotherapy if they were stable or responsive. The tumor volume had to be compatible with radiotherapy in a curative intent. Treatment was proposed as a compassionate option since no standard treatment is defined for patients with glioblastoma and severe deterioration of neurological functions. All patients and families were informed of the risks of bevacizumab, especially brain hemorrhages, and on the off-license use of bevacizumab in Europe for glioblastoma. All patients gave their informed consent and the Committee on Human Research from the institutions approved the study protocol.

All patients had a stereotactic or surgical biopsy. All had progressive and measurable contrast-enhancing tumor on MRI. Data were collected about patient and tumor characteristics, NS and cognitive functions throughout the evolution. Patients were classified in RPA V or VI class according to age, surgical resection, mini-mental status evaluation and WHO performance status.

Treatment consisted of intravenous bevacizumab 10 mg/kg over 90 min every 2 weeks, and oral temozolomide 150 mg/m²/day for 5 days for the first cycle, then 200 mg/m²/day for 5 days every month in the absence of CTCAE grade 2 or worse toxicity. In 2 patients, intravenous fotemustine 80 mg/m² was given every 2 weeks instead of temozolomide. Neoadjuvant treatment was pursued until maximal clinical and MRI response, and then a conventional radiotherapy (60 Gy in 30 fractions) was given according to current standards.

NS was recorded using the MRC criteria (NS 0: no alteration; NS 1: minor alteration; NS 2: mild alteration, kept autonomy; NS 3: marked alteration, assistance required; NS 4: severe alteration, complete assistance) [6]. Clinical and MRI responses were assessed according to the RANO criteria [7]. An independent radiologist reviewed responses on MRI. The progression-free survival (PFS) between the start of bevacizumab and the date of progression and/or intolerable toxicity and/or death was measured.

Results

Between August 2010 and May 2011, nine patients were offered bevacizumab as upfront treatment for de novo glioblastoma. All had major inaugural neurological signs (NS 3 or 4). One refused and was treated with temozolomide and radiotherapy. The pretreatment characteristics for the other 8 patients are given in [table 1](#). The mean age was 55.4 years. Two patients had a partial resection and 1 patient a complete resection, but tumor regrowth was rapid after surgery. Five patients had stereotactic biopsy only. According to the RTOG criteria, 5 patients were in RPA class V and 3 in class VI. Methylation of MGMT promoter was not determined. All patients received bevacizumab as upfront adjuvant treatment, but duration and associated cytotoxic drugs were not the same in this retrospective bicentric study ([table 2](#)).

Toxicity

Grade III–IV hematological toxicity was recorded for 2 patients who received temozolomide. In the first patient, the temozolomide dose was reduced; in the other one, temozolomide was stopped. No other toxicity was encountered.

Response to Treatment

The evolution of the NS under treatment is shown in [fig. 1](#). A clinical response was observed in 8/8 patients at the end of neoadjuvant bevacizumab, but only 4/8 were still responders after the completion of radiotherapy. Successive MRI of the most demonstrative response is shown in [fig. 2](#). Response combining MRI analysis and clinical responses according to RANO is shown in [table 2](#). In most patients, corticosteroid dose was tapered or even stopped. No transient radiological imaging abnormalities characteristic of pseudoprogression were seen after the end of concomitant chemoradiation. Overall survival was unusually high for these patients in RPA V–VI classes.

Discussion

In this short study, we have retrospectively evaluated the efficiency of upfront bevacizumab before radiotherapy in 8 patients with glioblastoma and severe impairment of NS at diagnosis.

All patients (8/8) experienced a neurological improvement after an average of 5 (1–6) injections of neoadjuvant bevacizumab and chemotherapy. However, only 4 maintained a clinical benefit after radiotherapy (2 with complete normalization of the neurological performance and 2 with partial improvement). The 4 other patients had no change (3) or deterioration (1). Toxicity was limited to neutropenia and thrombopenia in 2 patients.

The present results indicate that upfront bevacizumab with either temozolomide or fotemustine is feasible and provides a rapid clinical benefit in this population with a poor prognosis. Quality of life was improved and radiotherapy was conducted under better conditions. Bevacizumab is currently being assessed as first-line treatment for glioblastoma in several trials, but results are not yet available. However, patients with severe neurological impairment (WHO performance status 3 or 4) have not been included in these ongoing trials. Few series have been devoted to glioblastoma of RPA V–VI classes. Lou et al. [8] used upfront bevacizumab and temozolomide in 41 patients with unresectable or multifocal glioblastoma. Not all patients received radiotherapy. The authors reported a 25% response rate and a 5.2-month PFS. Treatment was well tolerated and the authors concluded that upfront therapy for unresectable or multifocal glioblastoma was an excellent platform to determine clinical activity. RPA V–VI classes regroup different situations. Some patients have multifocal or bulky disease that could never be irradiated at a curative dose (50–60 Gy) on the tumor field. In the others, tumor volume is compatible with radiotherapy at a curative dose but the tumor is located in a functional area. In such situations, bad general and neurological conditions hamper the planned radiotherapy. However, radiotherapy remains a major weapon against glioblastoma that must be used to obtain an increased survival [9].

Our short series provides a supplementary argument for the rapid use of an antiangiogenic drug when neurological conditions have deteriorated. We are planning a prospective clinical trial in which patients with severe alteration of NS due to a tumor location in a functional area will receive intravenous bevacizumab 10 mg/kg at a 2-week interval and a single course of oral or intravenous temozolomide (150 mg/m²/day for 5 days). If general or neurological conditions are stable or improved at 1 month, conventional radiotherapy (60 Gy in 30 fractions) will start with concomitant daily temozolomide 75 mg/m²/day, and bevacizumab 10 mg/kg every 2 weeks. Adjuvant treatment will consist of 6 monthly courses of temozolomide 200 mg/m²/day for 5 days, and bevacizumab every 2 weeks for 6 months.

Table 1. Characteristics of patients at diagnosis

Characteristics	n
Age, years	
30–39	1
40–49	2
50–59	1
60–69	3
70–79	1
Sex	
Male	3
Female	5
RTOG RPA	
RPA V	5
RPA VI	3
Extent of surgery	
Biopsy	5
Partial	2
Complete	1
Tumor localization	
Frontal	2
Parietal	2
Temporal	2
Parietooccipital	1
Temporoparietal	1
Neurological signs	
Confusional syndrome	1
Hemiplegia	5
Intracranial hypertension	2
Memory disorder	1
Disorder of vigilance	1

Table 2. Characteristics of and response to treatment

Patient, sex	Type of chemotherapy	BVB infusions before radiotherapy	BVB during radiotherapy	TMZ during radiotherapy	RANO response	Time to progression months	Survival months
1, F	TMZ/BVB	6	yes	yes	PR	14+	15+
2, M	TMZ/BVB	6	yes	yes	S	4	9
3, M	TMZ/BVB	1	yes	yes	CR	14	22+
4, M	TMZ/BVB	8	yes	yes	S	5	13+
5, M	TMZ/BVB	2	yes	yes	S	10+	11+
6, F	fote/BVB	5	no	no	S	4	13
7, F	TMZ/BVB	6	no	yes	S	6	11+
8, M	fote/BVB	5	no	yes	S	10	12

TMZ = Temozolomide; BVB = bevacizumab; fote = fotemustine; CR = complete response; PR = partial response; S = stability; + = response or survival ongoing at time of analysis.

Fig. 1. Evolution of NS according to the MRC score. A = Initial NS, before neoadjuvant bevacizumab and chemotherapy. B = After neoadjuvant treatment and before radiotherapy. C = Immediately after radiotherapy. D = 2 months after the end of radiotherapy.

Fig. 2. MRI of patient 1F, who had hemiplegia at diagnosis. Upper panel = T₁ + gadolinium. Lower panel = T₂ FLAIR. 1A, 2A = Before treatment. 1B, 2B = After neoadjuvant bevacizumab and temozolomide. 1C, 2C = 2 months after the end of radiotherapy. 1D, 2D = 12 months after the end of radiotherapy (whereas the neurological examination remained normal).

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