Glioblastoma in Tunisia: A retrospective study about 41 cases.

Glioblastome en Tunisie : Etude rétrospective à propos de 41 cas

Sonia Ben Nasr[1], Abderrazek Haddaoui[1], Slim Bach Hamba[2], Aymen Lagha[2], Soumaya Labidi[2], Mehdi Afrit[2], Farouk Benna[3], Hafedh Jmal[4], Hamouda Boussen[2].

1-Service d'oncologie médicale de l'hôpital militaire principal d'instruction de Tunis - Université Tunis El Manar-Faculté de Médecine de Tunis
2- Service d'oncologie médicale de l'hôpital Abderrahmane Mami de l'Ariana
3-Service de radiothérapie de l'institut Salah Azaiz de Tunis
4-Service de neurochirurgie de l'institut de neurologie-Hôpital la Rabta de Tunis

RÉSUMÉ

Prérequis: Le glioblastome (GB) est la tumeur cérébrale primitive la plus fréquente (25%) et mortelle des tumeurs cérébrales primitives de l'adulte. L'objectif de notre étude était de rapporter les caractéristiques épidémiologiques, cliniques et thérapeutiques du GB en Tunisie.

Méthodes: Etude rétrospective sur 41 cas de GB confirmé histologiquement traités entre 2006 et 2012 dans les services d'oncologie médicale de l'hôpital Abderrahmane Mami de l'Ariana et l'hôpital militaire de Tunis.

Résultats: L'âge médian était de 54 ans (13 à 72 ans) et le sexe-ratio était de 2,3. L'indice de Karnofsky (KPS) était <70% dans 31,7% des cas. La classe RTOG-RPA était III dans 11 (26,8%), IV dans 19 (46,3%), V dans 10 (24,3%) et VI dans 1 (2,4%) cas. Une résection complète (RC) était faite chez 29 patients (70,7%), une résection partielle (RP) ou une réduction tumorale chez 5 patients (12,2%) et une biopsie chez 7 patients (17,1%). Tous les patients ont reçu une radiothérapie (RT) cérébrale à une dose de 60 Gy concomitante avec le témozolomide (TMZ). Dix neuf patients (46,3%) ont reçu TMZ en adjuvant, 8 d'entre eux ont terminé 6 cycles. La survie globale (SG) médiane était de 12 mois (2 à 56 mois). La SG à 6, 12, 18, et 24 mois était de 84,6%, 57,6%, 35,4% et 20,7% et était corrélée à l'âge, au KPS, à la classe RPA et à la qualité de la résection.

Conclusion: Notre étude est la première série africaine sur le GB. Malgré qu'on a inclus des patients de mauvais pronostic avec une fonction neurocognitive altérée et malgré l'interruption du traitement adjuvant, la SG médiane était comparable à l'étude Stupp.

Mots-clés
glioblastome, chirurgie, témozolomide, radiothérapie, survie.

SUMMARY

Background: Glioblastoma (GB) is the most common and lethal primary brain tumor in adults representing 25% of primary brain tumors in adults. The objective of our study was to report the epidemiologic, clinical and therapeutic features of GB in Tunisia.

Methods: Our retrospective study included 41 patients with histologically confirmed GB treated between 2006 and 2012 at the medical oncology departments of Abderrahmane Mami hospital in Ariana and the military hospital in Tunis.

Results: Median age was 54 years (13 to 72 years) and sex-ratio was 2.3. Karnofsky performance status (KPS) was <70% in 31.7% of cases, while Recursive partitioning analysis radiation therapy oncology group (RTOG-RPA) classification was III in 11 (26.8%), IV in 19 (46.3%), V in 10 (24.3%) and VI in 1 (2.4%) cases. Complete resection (CR) was achieved in 29 patients (70.7%), partial resection (PR) or tumor debulking in 5 patients (12.2%) and biopsy alone (BA) in 7 patients (17.1%). All patients received brain radiotherapy (RT) at a dose of 60 Gy combined with concurrent temozolomide (TMZ). Nineteen patients (46.3%) received adjuvant TMZ, 8 of them completed 6 cycles. Median overall survival (OS) was 12 months (2 to 56 months). Six, 12, 18 and 24-months OS rates were 84.6%, 57.6%, 35.4% and 20.7%, OS being correlated to age, KPS, RPA and quality of resection.

Conclusion: Our retrospective study is the first African GB series. Despite it included predominantly poor prognosis patients with impaired neurocognitive function and adjuvant treatment discontinuation, our median OS was comparable to Stupp data.

Key-words
Glioblastoma, surgery, temozolomide, radiotherapy, survival.

Glioblastoma (GB) is the most frequent and most lethal primary brain tumor in adults representing 25% of primary brain tumor in adults and the most lethal brain cancer (1). Its incidence increased during the last 30 years but recent improvements such as imaging, histological classifications and chemotherapy (CT) with oral temozolomide (TMZ) combined with radiotherapy (RT) have lead to a modest but significant survival increase (2-4). The objective of our retrospective study was to report the epidemiologic profile, clinical and surgical features and therapeutic results in patients treated for GB in Tunisia.

METHODS

This retrospective study evaluated medical records of 41 patients with histologically confirmed GB, treated between 2006 and 2012 at the medical oncology departments of Abderrahmane Mami hospital in Ariana and Tunis military hospital. We analyzed initial symptoms, Karnofsky performance scale (KPS) and prognostic classes using Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG-RPA) scale (5). Most of them had been surgically resected before orientation to medical oncology for standardized RT/CT protocol. The extent of macroscopic resection was defined by neurosurgeon as complete resection (CR), partial resection (PR) and biopsy alone (BA) according to intraoperative evaluation and features on early postoperative MRI (POMRI) performed 24-72 hours after surgery. CR consisted of more than 98% of tumor removal without contrast enhancement on MRI. PR was defined as more than 50% of tumor ablation and presence of contrast enhancement on POMRI, while some patients had BA generally by stereotaxic (6). Treatment protocol included oral TMZ concurrently with postoperative RT. RT was performed by cobalt machines of linear accelerator, based on bidimensional conformal planning techniques at a programmed dose of 60 Gy in 30 fractions of 2 Gy. TMZ dose was daily 75 mg/m2 for concomitant schedule, 5 days per week during RT and daily150-200 mg/m2 5days/cycle for 6 28 days cycles (7). Patients were followed-up over the course of their adjuvant TMZ and further MRI with contrast was performed at 1 month post chemoradiotherapy and 3 months thereafter to assess the extent of the disease and evidence of any recurrence. Methylation status of O6 methylguanine DNA transferase (MGMT) was not performed due to technical reasons. Tumor progression was defined according to the modified RANO criteria as an increase in tumor size by 25 percent, the appearance of new lesions, or an increased need for corticosteroids (8). For statistical analysis, the data were analyzed using SPSS Version 18 software. We calculated frequencies and relative frequencies (percentages) for qualitative variables and means and medians for quantitative variables. We estimated overall survival (OS) curves with the Kaplan-Meier method and compared with the log-rank test.

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RESULTS

We treated 41 patients with histologically confirmed GB representing 0.8% of the cohort of cancer patients treated during the same period at our institutions. Their median age at diagnosis was 54 years (range 13–72 years). The most common symptoms were signs of raised intracranial hypertension in 19 cases (46.3%), hemiplegia or hemiparesis in 12 cases (29.2%), and seizures in 7 patients (17%). KPS was less than 70 in 13 patients (31.7%) while RPA classification was III in 11 (26.8%), IV in 19 (46.3%), V in 10 (24.3%) and VI in 1 (2.4%).

CR was achieved in 29 patients (70.7%), PR in 5 patients (12.2%), and BA in 7 patients (17.1%). All patients received brain RT of 60 Gy combined with TMZ and 19 of them (46.34%) were treated by adjuvant TMZ, 8 of them completing the scheduled 6 cycles. Patients didn't have or didn't continued adjuvant TMZ due to disease progression in 5 (12.2%), death in 5 (12.2%), KPS deterioration in 4 (9.75%) and grade 4 hematologic or nonhematologic toxicity in 19 (46.34%) patients. Most of the patients were under corticosteroids and anticonvulsant. With a median follow-up of 12 months (2-56 months), 8 patients relapsed (19.5%). 4 of relapsing patients received a second line CT including Carboplatin and Etoposide in 2, TMZ and Irinotecan in 1, Bevacizumab in 1;the remaining 4 received again TMZ alone.

Median overall survival OS was 12 months (2-56 months) and 6, 12, 18, and 24-month overall survival rates were 84.6%, 57.6%, 35.4% and 20.7% respectively (figure 1). Significant parameters influencing OS were age <60 years and >60 years (15.5 versus 8.5 months; p=0.01) (figure 2), Recursive partitioning analysis radiation therapy oncology group (RTOG-RPA) class III-IV vs V-VI (14.5 versus 7 months; p<0.0001) (figure 3), KPS >70% vs KPS <70% (15 versus 9 months; p<0.0001) (figure 4) and quality of surgical resection CR vs PR and BA (15 versus 8.5 months; p=0.01) (figure 5). Five patients were long term survivors (OS longer than 3 years after initial craniotomy). OS was 56 and 48 months in 2 men and 45, 36 and 36 months in 3 women. Four of them are still alive. The favorable subgroup was characterized by a younger median age (27 years versus 56 years), a higher percentage of female patients (M:F-ratio = 0.66 versus 2.66), a higher median post-operative KPS (90 versus 70). One of them had tumor recurrence 33 months after treatment.

Figure 1: Overall survival of all study population

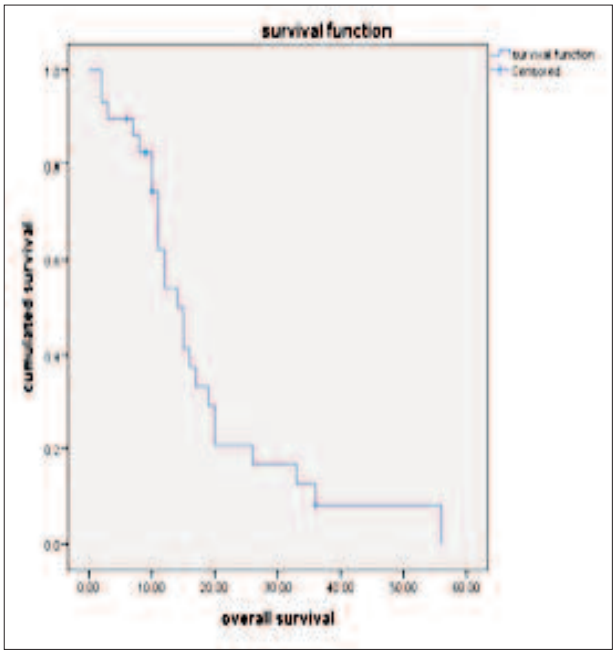


Figure 2: Overall survival according to age more or less than 60 years (p=0.01)

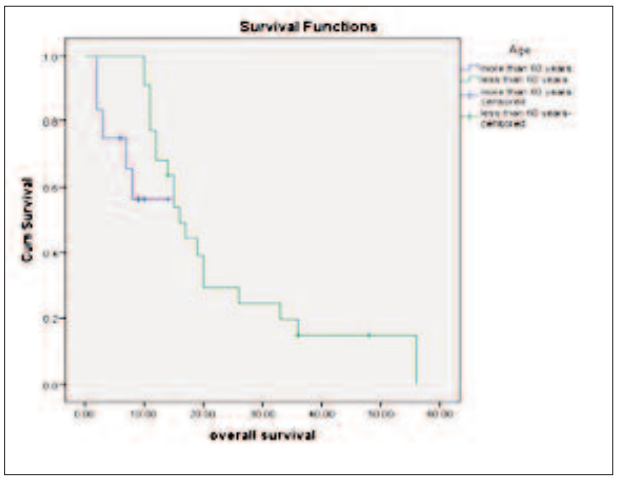


Figure 3: Overall survival according to RPA III, IV or V, VI (p<0.0001)

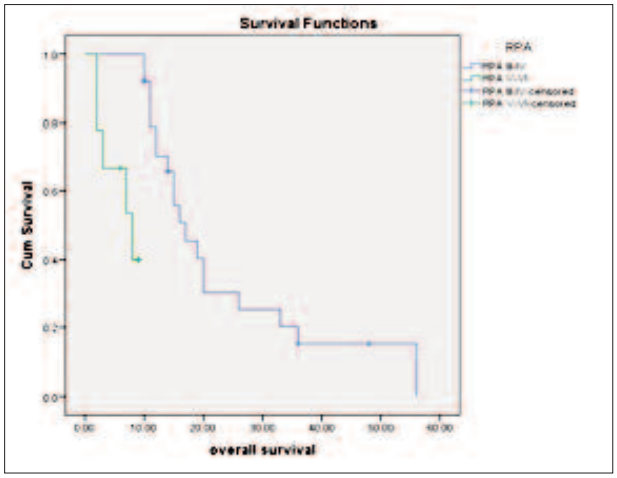


Figure 4: Overall survival according to KPS more or less than 70% (p<0.0001)

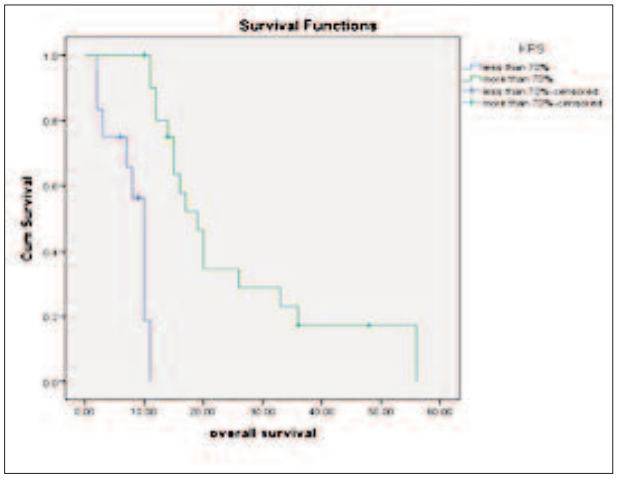
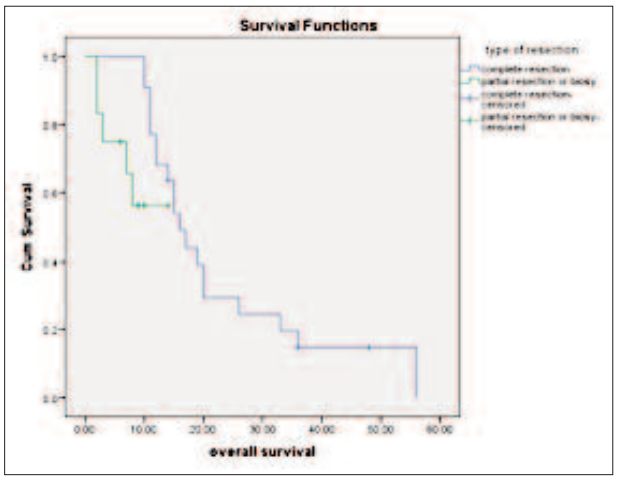


Figure 5: Overall survival according to type of resection (p=0.01)



DISCUSSION

36.5% of our patients were aged 60 years or more and only one patient (2.4%) was a child aged 13 years, data in accordance with literature, pediatric cases being rare (1, 9). Young patient age and high patient performance are generally accepted independent factors of prolonged survival. A recent study reported that age threshold of 60 years is most appropriate to separate good and poor prognosis patients probably due to presence of co-morbidities and more sequelae after surgery (10). In our study, patients aged more than 60 years had better OS than those aged less than 60 years (p=0.01) with a median OS of 15.5 months vs 8.5 months. KPS was less than 70% in 31.7% of patients. OS was significantly better in patients with KPS more than 70% than in those with KPS less than 70% with median OS of 15 months vs 9 months. In the literature, a minimum score of 70 is usually required to qualify patients for aggressive treatment and is significantly associated with a favorable prognosis (2). As seen in our study, localization signs and neurocognitive troubles are the most common symptoms (9). Patients that present with acute onset of disabling symptoms such as stroke-like presentations or seizures demonstrate an improved survival when compared to those patients with more subtle symptoms that gradually evolve over time (2).

In contrast to patient age and performance, the prognostic impact of the extent of tumor resection remains uncertain (10,11) despite the fact that in our series, OS was significantly better in patients having had CR than those who had PR or BA (p=0.01) with a median OS of 15 months vs 8.5 months. Recently, Stummer et al (12) provided level 2b evidence that survival depends on CR of enhancing tumor, after adjustment for biases. A significant association between the extent of tumor resection and survival has also been shown in several retrospective studies in uni- and/or multivariate analysis (1,9,12). Current protocols suggest that standard treatment of patients with a GBM should include maximal neurosurgical resection balanced against the preservation of neurological function. Palliative cytoreductive surgery is an option for providing relief in neurological symptoms. Although maximal surgical resection may improve survival, it is not always possible due to the infiltrative nature of the tumour or

its location within eloquent areas and therefore debulking of the tumour or even biopsy alone may be the only available surgical options. CR is done in 36% in recent studies. A phase III study demonstrated an increase in complete resection when using fluorescence (13). In our study, CR was achieved in 29 patients (70.7%), PR in 5 patients (12.2%), and BA in 7 patients (17.1%). Because of the infiltrative nature of the tumour, further postoperative treatment is required to prevent or delay tumour recurrence. In 2005, a phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) showed the benefit of adding TMZ during and after radiotherapy treatment in GBM and thus defined the new standard of care in this devastating disease. This schedule increased the median OS from 12.1 to 14.6 months and the two-year survival rate from 10.4 to 26.5%, with a good tolerance profile (7). Moreover, methylation of the promoter of the O6 methylguanine DNA transferase (MGMT) gene exhibits a prognostic impact independently of therapeutic schedule but may also predict the benefit of adding TMZ to RT. However, pitfalls in MGMT determination and lack of prospective validation have to be solved before considering MGMT as a decisional marker (9). In our study patients had concurrent radiochemotherapy with TMZ regardless of MGMT status. Radiation dose and adjuvant TMZ are independent prognostic factors for OS (1). In the present study, patients were treated with RT combined with TMZ and the majority received the optimal or acceptable radiation dose. Most patients were treated with cobalt 60 teletherapy because of lack of linear accelerator in many radiotherapy centers. At a median follow-up of 12 months, 24 patients (58.5%) died. Median overall survival was 12 months (2-56 months) and two-year survival rate was 20.7%. Overall survival in GBM is usually <12 months after surgery and RT and long-term survival is rare (3-5%) (1,14). Long term survival are usually female predominant, younger than 60 years, having a good initial functional score and having a combination of CR, RT and CT (14). In our study, few patients (12.2%) corresponded to this favorable profile explaining the high recurrence level of 8 patients (19.5%). 4 of them received second line CT including Carboplatin and Etoposide in 2, TMZ and Irinotecan in 1 and Bevacizumab in 1 patient. 4 patients returned to TMZ alone. Only 1 patient had third line treatment (Bevacizumab). TMZ at recurrence has limited but significant efficacy with 5% of objective response and event free survival at 6 months of 21% compared to 8% with procarbazine (p=0.008) (9). In 2007, a phase II trial had reported that bevacizumab and irinotecan (CPT11) was an effective treatment for recurrent glioblastoma with a moderate toxicity marked by thromboembolic events (15). The BRAIN multicenter trial randomly assigned patients with glioblastoma previously treated with TMZ-based chemoradiation into bevacizumab alone or bevacizumab plus CPT11 until disease progression. Estimated 6-month progression free survival rates were 42.6% and 50.3% in the bevacizumab alone and the combination groups, respectively and a median OS of 9.2 and 8.7 months, respectively. Severe toxicities were more frequent in the arm CPT11-bevacizumab (65.8%, versus 46.4%) (4,15).

CONCLUSION

Our retrospective study is the first African GB series. Despite it included predominantly poor prognosis patients with impaired neurocognitive function and adjuvant treatment discontinuation due to toxicity and KPS deterioration, our median OS was comparable to Stupp data. According to our findings and review of the literature, GBM is still a highly violent tumor that tends to have early relapse and short-term survival. Multimodality therapy including safe optimal surgical resection combined by adjuvant radiotherapy or concurrent chemoradiation and sequential chemotherapy is recommended for all patients. Despite modest improvement in the overall survival of patients with GBM in the recent decade, the outcome remains poor. Therefore, the need for more effective novel treatments in this neoplasm is urgently needed.

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