Prognosis of glioblastoma patients improves significantly over time interrogating historical controls

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Key words

Glioblastoma, Survival analysis, Prognosis, Isocitrate Dehydrogenase, Standard of care, Palliative care

Abstract

Background: Glioblastoma (GBM) is the most common devastating primary brain cancer in adults. In our clinical practice, median overall survival (mOS) of GBM patients seems increasing over time.

Methods: To address this observation, we have retrospectively analyzed the prognosis of 722 newly diagnosed GBM patients, aged below 70, in good clinical conditions (*i.e.* Karnofsky Performance Status – KPS- above 70%) and treated in our department according to the standard of care (SOC) between 2005 and 2018. Patients were divided into two groups according to the year of diagnosis (group 1: from 2005 to 2012; group 2: from 2013 to 2018).

Results: Characteristics of patients and tumors of both groups were very similar regarding confounding factors (age, KPS, *MGMT* promoter methylation status and treatments). Follow-up time was fixed at 24 months to ensure comparable survival times between both groups. Group 1 patients had a mOS of 19 months ([17.3-21.3]) while mOS of group 2 patients was not reached. The recent period of diagnosis was significantly associated with a longer mOS in univariate analysis (HR=0.64, 95% CI [0.51 – 0.81]), p<0.001). Multivariate Cox analysis showed that the period of diagnosis remained significantly prognostic after adjustment on confounding factors (adjusted Hazard Ratio (aHR) 0.49, 95% CI [0.36-0.67], p<0.001).

Conclusion: This increase of mOS over time in newly diagnosed GBM patients could be explained by better management of potentially associated non-neurological diseases, optimization of validated SOC, better management of treatments side effects, supportive care and participation in clinical trials.

Background

Glioblastoma (GBM) is the most frequent and aggressive primary malignant brain tumor in adults.[1] Indeed, the annual incidence is 3-4 per 100 000 people.[2,3]

Standard of care (SOC) of newly diagnosed GBM patients, aged below 70 years in good clinical conditions (*i.e.* Karnofsky Performance Status –KPS- above 70), is a maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide (RT/TMZ+TMZ).[4] It was introduced in 2005 and consists of a focal irradiation of 60 Gy in daily fractions of 2 Gy and continuous daily temozolomide from the first to the last day of radiotherapy followed by six monthly cycles of adjuvant temozolomide.

This treatment has allowed median overall survival (mOS) to increase from 12 months to 14.6 months.[4–6] The 2 years OS is 25-27% and 5 years OS is 5.5%.[2]

Age, performance status, *MGMT (O6-methylguanine DNA-methyltransferase*) promoter methylation and *IDH* mutational status are established as robust prognostic factors used as inclusion criteria or stratification factors in clinical trials.[7–9]

In the recent update of the World Health Organization (WHO) classification of tumors of the central nervous system, the term "GBM" is dedicated to *IDH*-wildtype (wt) tumors, while astrocytomas WHO grade 4 *IDH*-mutant (mt) are no longer termed GBM[10]. Consequently, we focused in this study on *IDH*-wt GBM patients.

Since the establishment of the RT/TMZ+TMZ protocol as SOC in 2005, no major advance has been done in the treatment of GBM patients. In 2009, Bevacizumab was shown to increase progression free survival (PFS) of GBM patients but without significant benefit on OS in first line and in recurrent settings.[11–14] More recently, tumor treating fields (TTF) and combination of Lomustine plus TMZ have shown significant efficacy in specific subpopulations of patients (*i.e.* patients in good clinical conditions after full completion of concurrent chemoradiation phase and patients with *MGMT*-promoter methylated GBM respectively).[15,16]

In contrast, there is no SOC for recurrent disease. Repeated surgery and re-irradiation may improve survival in some patients when feasible.[17] Lomustine, Bevacizumab and Carboplatin are the main systemic treatments for recurrent GBM.[18,19]

Multidisciplinary supportive care has also noticeably improved over the last decades with close consideration as meaningful endpoints of quality of life, management of symptoms and management of therapeutic side effects.

The aim of the current study was to evaluate whether prognosis of newly diagnosed GBM patients has improved since 2005 (the date when the SOC was published and widely used).[4]

Materials and Methods

Population

Patients were selected retrospectively from neuro-oncology database (OncoNeuroTek) according to the following criteria: (i) newly diagnosed histologically confirmed GBM diagnosed between 2005 and 2018, (ii) primarily treated by RT/TMZ+TMZ protocol,[4] (iii) under or equal 70 years old and, (iv) KPS ≥ 70. All patients were diagnosed at Pitié-Salpêtrière hospital, Paris, France.

For each patient we have collected age at diagnosis, KPS[20–22], *IDH* mutation status (mt or wt), *MGMT* promoter methylation status, the extent of the initial surgery (biopsy/partial resection/complete resection), surgery at relapse (yes/no), the number of lines of treatment, treatment with Bevacizumab (yes/no), treatment received after the first tumor progression (TMZ +/- Lomustine +/- Bevacizumab *versus* other) and the date of death or the date of the last clinic visit for patients still alive at the time of data collection (Table 1, Supplementary Table 1). *IDH*-mt tumors or tumors for which *IDH* mutational status was unknown were excluded from our cohort.

Molecular markers

The presence of IDH1 Arg132His (IDH1 R132H) mutation was determined by immunohistochemistry with a mutation-specific antibody - IDH1 (Clinisciences ; R132H ; 1/100ème) - on paraffin-embedded tissue sections (FFPE).[23] For patients under 55 years of age and diagnosed from 2009, when IDH1 R132H immunohistochemistry was negative the mutational status of *IDH1* and *IDH2* was then determined using the Sanger sequencing technique or DNA next generation sequencing[24], as previously described.[7] According to the 2021 WHO classification of brain tumors, patients over or equal 55 years old were considered *IDH*-wt if IDH1 R132H immunostaining was negative.[3]

Promoter methylation status of *MGMT* was assessed on DNA isolated from FFPE tumor samples obtained at initial surgery. It was determined by bisulfite modification and subsequent nested methylation-specific polymerase chain reaction, a two-stage polymerase chain reaction approach, as previously described.[25]

Statistical analysis

Continuous variables were described as mean and standard deviation, and categorical variables were described as frequencies (%).

Two groups of patients were constructed according to the year of diagnosis of their disease: group 1 (between 2005 and 2012) and group 2 (between 2013 and 2018). The cut-off was 2012 as it is the year that most balanced the number of events (deaths) between the groups.

OS was estimated by the Kaplan Meier curve. To be able to compare the two period groups, the follow-up time was set for all patients at 24 months (administrative censoring). A log-rank test was performed to compare the OS across groups. Univariate and multivariate cox models were built from the following factors: period of diagnosis (2005-2012 vs 2013-2018), age, KPS score, *MGMT* promoter methylation status, the extent of the initial surgery and surgery at relapse as time dependent variable to avoid immortal bias.[26] The missing values of *MGMT* promoter methylation status were handled using multiple imputation (20 generated samples). The Cox assumptions (log-linearity and proportional hazard ratio) were checked for all variables. Results were reported as adjusted hazard ratios (aHR), with their 95% confidence interval (95% CI).

Two sensitivity analyses were performed. The first concerned missing *MGMT* promoter methylation status data: cox models were built without multiple imputation and omitting missing *MGMT* promoter methylation status data and the second sensitivity analysis concerned the period of diagnostic: replacing the period of diagnosis (dichotomous variable) by the year of diagnosis (continuous variable) to avoid the threshold effect.

Analyses were performed with R version 4.1.0. All tests were two-tailed and p values < 0.05 were considered statistically significant.

Results

From OncoNeuroTek database, 722 patients fulfilled the inclusion criteria from 2005 to 2018. The data cut-off date was 2012.

The mean age at diagnosis was 56 years and 50% of patients have a KPS superior to 90% (Q1-Q3: 80-90). *MGMT* promoter methylation status was available for 217 patients (30.05%), of which 97 (44.7%) had a methylation of *MGMT* promoter. At the time of relapse, 104 patients (14.4%) underwent surgery (Table 1).

All patients were treated with RT/TMZ+TMZ protocol in first line setting as it is the SOC.

311 patients were diagnosed from 2005 to 2012 and 411 patients diagnosed from 2013 to 2018.

Age, KPS, *MGMT* promoter methylation status and surgery at relapse were evenly distributed among the two groups (Table 1). The number of lines of treatment was significantly higher in patients diagnosed from 2005 to 2012 than those patients diagnosed from 2013 to 2018 (with a PFS rate at 24 months of 33.1% [27.9-39.2] and 43.4% [37.4-50.3] respectively), while the number of patients receiving bevacizumab was evenly distributed among the 2 groups (Table 1).

Pre-cut-off survival results (raw data) are shown in Figure 1.

Significantly longer OS were observed for patients diagnosed in 2013-2018 than those diagnosed in 2005-2012 ($p<0.0001$) (Figure 2).

Cox univariate analysis found KPS, *MGMT* promoter methylation status (methylated vs unmethylated), period of diagnosis (2005-2012 vs 2013-2018) and the extent of initial surgery to be significant prognostic factors affecting OS (respectively HR=0.72, 95% CI [0.62-0.83], $p<0.001$; HR=0.36, 95% CI [0.24-0.55]); HR=0.64, 95% CI [0.51-0.81], $p<0.001$; HR=0.50, 95% CI [0.36-0.70] and HR=0.61, 95% CI [0.47-0.81], $p<0.001$) (Table 2).

Multivariate Cox analysis showed that the period of diagnosis remained significant after adjustment on confounding factors such as age, KPS, the extent of the initial surgery, surgery at relapse and *MGMT* promoter methylation status (Figure 3, adjusted Hazard Ratio (aHR) 0.49, 95% CI [0.36-0.67], $p<0.001$). The risk of death was decreased by 51% when patient was diagnosed after 2012 compared to patient diagnosed before 2013 (Table 3 and Figure 2).

Sensitivity analysis regarding how to deal with *MGMT* promoter methylation status missing data have shown the same results (adjusted HR of the year of diagnosis 0.47, 95%CI [0.28-0.79], p=0.004).

When considering the year of diagnosis as a quantitative variable (+3 years), its impact on OS remained significant (aHR=0.76, 95% CI [0.67-0.86], p<0.001). The fact that the diagnosis was made 3 years later decreased the risk of death by 24% compared with the patient whose diagnosis was made at time t, this result was adjusted on age, KPS and *MGMT* promoter methylation status and the extent of the initial surgery (Table 4).

Discussion

In this monocentric large-scale population of newly diagnosed GBM patients we found a statistically significant improvement of OS by 51% in patients diagnosed from 2013 to 2018 compared to those diagnosed from 2005 to 2012, consistent with clinical practice observations. The significant improvement of OS of newly diagnosed GBM patients over time was confirmed when considering the year of diagnosis as a quantitative variable, with an improvement of OS by 24% for each additional 3 years of diagnosis.

In our population, patients were aged 70 years old or below and had a KPS superior or equal to 70% according to the population enrolled in the pivotal phase 3 clinical trial that has established the SOC.[4] They were treated with RT/TMZ+TMZ protocol as first-line treatment.

In the literature, known prognostic factors affecting OS of GBM patients and used as stratification/inclusion criteria in clinical trials are age, KPS and *MGMT* promoter methylation status[25,27]. Regarding surgery at relapse, it is admitted that this procedure might improve post-recurrence survival in patients who are candidates for gross total resection of enhancing tumor[17]. Recently, European Association of Neuro-Oncology (EANO) guidelines on the treatment of diffuse gliomas recommend that second surgery should be considered in all patients at relapse[28].

In our study of GBM patients < 70 years old and with a KPS ≥ 70%, age, KPS, extent of resection at initial surgery and *MGMT* promoter methylation were found as prognostic factors affecting OS in multivariate analysis (Table 3, Table 4). The occurrence of a surgery at the time of relapse was not significantly associated with OS (Table 2). Interestingly, prognostic factors were balanced over time in our two populations (groups 1 and 2).

MGMT promoter methylation status was available only for 217 patients. In our study, 44.7% of patients had a methylated *MGMT* promoter, in accordance with the existing literature.[8] The presence of missing values remains a challenge. MGMT testing was significantly lower in group 2 compared to group 1 (39.9% vs 22.6%, $p < 0.001$). This difference can be primarily attributed to the fact that patients in group 2 were significantly more likely to have had a biopsy at the time of initial surgical management (Table 1), with less material available for molecular analysis. Furthermore, there is no clinical reason that the proportion of MGMT-methylated GBM patients changes dramatically between group 1 and group 2. Moreover, the imputations in the statistical analyses do not indicate any significant impact of the difference of proportion

of MGMT testing in the prognostic analysis. Missing data replacement was performed using multiple imputation. This method is well known in the literature for its ability to reduce prediction error of missing values, and to consider uncertainty by creating different versions of completed datasets. Sensitivity analysis confirmed the trend of the improvement of OS over time. It is worth noting that the percentage of patients in each *MGMT* status category after imputation is similar and follows the same trend as the observed data. Thus, multiple imputations did not introduce any additional bias. Furthermore, the results of the two models (before and after imputation) are very close (Supplementary Figure 1 and Supplementary Table 2).

Our study found a mOS of 19-25.8 months whereas historical data of GBM patients with clinical, molecular and treatment aspects similar to our population reported OS of 15-16 months.[4,6] Of note, the original EORTC study enrolled patients with WHO 0-2 performance status, which included KPS ≥ 60%.[4] This may have a small impact on the findings since the patients included in the present study have KPS≥70%. Although the number of patients is lower compared to our study, a similar trend is observed in prospective clinical trials (mOS of 20.4 months[29] and 21.2 months[30]) and a recent phase 3 clinical trial has also shown an increase of mOS of *MGMT* methylated newly diagnosed GBM patients reaching 32.1 months.[31]

Possible explanations of this improvement in GBM survival between our recent population and previous populations include neurosurgical advances,[27] potential earlier diagnosis, antitumoral treatments at relapse and supportive care. Participation in clinical trials may also contribute to survival improvement.

In our population, antitumoral molecules used at relapse were bevacizumab, irinotecan, lomustine, carmustine, and carboplatin. There is no SOC at relapse, but lomustine, bevacizumab and carboplatin are the main systemic treatments for recurrent GBM.[18,19] Although these drugs have never demonstrated OS benefit in randomized phase 3 clinical trials, some patients get clinical benefit with tumor response and increased PFS that may be converted into OS benefit. Interestingly, 24.5% of group 1 patients were treated with irinotecan and bevacizumab at relapse, whereas none of group 2 patients received this treatment and the predominant treatments at relapse in group 2 patients were lomustine, carboplatin and bevacizumab. Multiple clinical trials investigating innovative drugs have been conducted over the study period. Even if the tested molecules did not all show a significant improvement in GBM patients' survival,

being included in a clinical trial constitutes, in and of itself, a good prognostic factor (due to the optimal clinical follow-up and supportive care in the context of a clinical trial).

Supportive care in GBM patients consist mainly in management of headache, epilepsy, veinous thromboembolism, mood swings, cognitive impairment, fatigue, nausea/vomiting and hematological disorders.[32]

Improvement in symptomatic treatments has also led to a better management of side effects of antitumor treatments, and thus to a decrease in the proportion of toxic deaths.

Palliative care alone has shown, in randomized controlled trials, to be associated with improvements in quality of life, mood, caregiver distress, and a less aggressive pattern of care at the end of life.[33] A phase 3 clinical trial also suggests a clinically meaningful survival benefit of early palliative care added to SOC compared to SOC alone in patients with non-small cell lung carcinoma.[34]Interestingly, this question will be specifically addressed in the GBM patients population in the setting of the EPCOG phase 3 clinical trial [35].

Our results of survival improvement over time in GBM patients are consistent with the pre-existing literature.[27,36,37] To our knowledge, this is the first study showing a survival improvement over time in GBM patients treated by RT/TMZ+TMZ protocol as first line treatment. Our results highlight that the use of historical controls can amplify the benefit of investigational therapeutic. Therefore, randomized clinical trials or the use of contemporary control cohorts are recommended to assess the potential benefit of novel investigational product. The limitations of our study are its retrospective and monocentric aspects, and an important number of missing data in *MGMT* promoter methylation status. The evolution of first line treatment (i.e. optimization of surgery, radiotherapy and chemotherapy), the evolution of second line and subsequent antitumoral treatments (i.e. re-surgery, re-irradiation and chemotherapy), management of potentially associated non-neurological disease, supportive care implemented as earlier as possible in the disease course, management of chemotherapeutic side effects, closer follow-up involving additional health professionals (i.e. practitioner nurses) and participation in clinical trials may explain at least partially this improvement of OS in GBM patients over time.

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