Combining intraoperative carmustine wafers and Stupp regimen in multimodal first-line treatment of primary glioblastomas

Vladislav Pavlov1,2,3, Philippe Page1,2, Georges Abi-Lahoud1,2, François Nataf1,2, Edouard Dezamis1,2, Audrey Robin4, Pascale Varlet2,3, Baris Turak1,2, Frédéric Dhermain5, Julien Domont6, Guillaume Louvel5, Raphaëlle Souillard-Scemama2,7, Eduardo Parraga1,2, Jean-François Meder2,7, Fabrice Chrétien2,3, Bertrand Devaux1,2* & Johan Pallud1,2*

1Department of Neurosurgery, Sainte-Anne Hospital, Paris, France, 2Paris Descartes University, Paris, France, 3Department of Neuropathology, Sainte-Anne Hospital, Paris, France, 4Department of Pharmacy, Sainte-Anne Hospital, Paris, France, 5Department of Radiation Oncology and Physics, Institut Gustave Roussy, Villejuif Cedex, Paris, France, 6Department of Medicine, Institut Gustave Roussy, Villejuif Cedex, Paris, France, and 7Department of Neuroradiology, Sainte-Anne Hospital, Paris, France

Abstract

Background. The study investigated if intraoperative use of carmustine wafers, particularly in combination with Stupp regimen, is a viable and safe first-line treatment option of glioblastomas. Methods. Eighty-three consecutive adult patients (50 men; mean age 60 years) with newly diagnosed supratentorial primary glioblastomas that underwent surgical resection with intraoperative carmustine wafers implantation (n = 7.1 ± 1.7) were retrospectively studied. Results. The median overall survival (OS) was 15.8 months with 56 patients dying over the course of the study. There was no significant association between the number of implanted carmustine wafers and complication rates (four surgical site infections, one death). The OS was significantly longer in Stupp regimen patients (19.5 months) as compared with patients with other postoperative treatments (13 months; p = 0.002). In addition patients with eight or more implanted carmustine wafers survived longer (24.5 months) than patients with seven or less implanted wafers (13 months; p = 0.021). Finally, regardless of the number of carmustine wafers, median OS was significantly longer in patients with a subtotal or total resection (21.5 months) than in patients with a partial resection (13 months; p = 0.011). Conclusions. The intraoperative use of carmustine wafers in combination with Stupp regimen is a viable first-line treatment option of glioblastomas. The prognostic value of this treatment association should be evaluated in a multicenter trial, ideally in a randomized and placebo-controlled one.

Keywords: carmustine wafers; glioblastoma; Stupp regimen; survival

Introduction

Glioblastoma multiforme [GBM, World Health Organization (WHO) grade IV astrocytoma] is the most common malignant primary brain tumor in adults and among the most aggressive of all tumors.1,2 The current standard post-surgery for patients with newly diagnosed GBM consists of concomitant chemoradiotherapy followed by adjuvant maintenance chemotherapy with temozolomide (TMZ), the so-called Stupp regimen.3,4 However, as an alternative treatment, biodegradable wafers impregnated with the cytotoxic agent carmustine (1,3-bis(2-chloreoethyl)-1-nitrosourea = BCNU), can be implanted in the surgical bed on the walls of the resection cavity for newly diagnosed and recurrent high-grade gliomas.5,6 Neither of these unimodal treatments7 have shown promising results. Multimodal treatment options that combine therapies are needed. Combining carmustine wafers (Gliadel®, MGI Pharma, Bloomington, MN, USA) with the Stupp regimen is one such multimodal option. Some retrospective8–12 and prospective13,7 studies combining these modalities have had interesting findings. These studies have reported 18-month median overall survival (OS) without a significant increase in complications or adverse events. In addition, a recent prospective study of progression-free survival (PFS) showed that surgery, carmustine wafers, radiotherapy, and 6-month metronomic TMZ chemotherapy produced promising results without a marked increase in toxicities as compared with the Stupp regimen.14 However, the literature on the use of carmustine wafers in addition to the Stupp regimen is still limited and as a practical consequence, the use of intraoperative carmustine wafers still
depends mainly on the neurosurgeon’s preferences. To add to this limited literature on multimodal therapies for GBMs, here, we present a retrospective observational monocentric study. The study reports on an 8-year long single-institution experience of treating adult patients with intraoperative carmustine wafers implantation during first-line treatment of GBM. Specifically, we addressed the efficacy and toxicity of carmustine wafers, particularly when associated with the Stupp regimen.

**Materials and methods**

**Data source**

We reviewed records of 405 adult patients diagnosed with GBM who were treated at Sainte-Anne University Hospital, Paris, France, between March 2004 and January 2012. To be included in the study patients needed to meet the following criteria: (1) over 18 years of age at diagnosis, (2) histological diagnosis of new-diagnosed primary GBM (WHO grade IV astrocytoma, secondary GBM excluded by an IDH1-positive immunohistoexpression) based on a central neuropathological review (PV), (3) supratentorial hemispheric location, (4) surgical resection with intraoperative carmustine wafers implantation without fluorescence-guided resection using 5-aminolevulinic acid, (5) minimal follow-up over the next 12 months from date of surgery, except in cases of progression or death. All enrolled patients gave their written informed consent for storage of the surgical samples for further analyses.

**Data collection**

Clinical and imaging characteristics collected at the time of histopathological diagnosis included: gender, age, neurological deficit, Karnofsky performance status (cutoff 70), main T1-weighted sequence contrast-enhanced tumor anatomical location (enhanced contrast obtained through injection of gadopentetate dimeglumine), contrast-enhanced tumor ventricular contact area and contrast-enhanced tumor volume (cutoff 40 cm³). The revised RTOG-RPA classification system for GBM was used retrospectively to stratify comprehensive clinical risk. This was done by classifying each patient (while blinded to patient survival) according to the RTOG-RPA classification system using the data collected at the time of histopathological diagnosis.

Neuropathological characteristics obtained from patient records included the histopathological GBM subtype: pleomorphic cell GBM, gliosarcoma, giant cells GBM, GBM with oligodendroglial component and small cell GBM. These characteristics were assigned according to the 2007 WHO classification of tumors of the central nervous system (CNS). The research of IDH1 R132H mutation was retrospectively performed by immunohistochemistry. The O-6-methylguanine-DNA methyltransferase (MGMT) methylation status and the MGMT expression by immunohistochemistry were not available for the patients under study.

Tumor-related characteristics obtained from patient records included: number of carmustine wafers implanted (cutoff of maximum of eight wafers), quantification of the extent of surgical resection based on early postoperative MRIs (within 48 h) on T1-weighted sequence following injection of gadopentetate dimeglumine, postoperative non-surgical and surgical complications (new neurological deficit or worsened neurological condition, seizures, postoperative hematoma requiring surgical evacuation, wound infection, meningitis, abscess), postoperative oncological treatments [none, radiotherapy alone, chemotherapy with TMZ alone, other chemotherapy alone, concomitant chemoradiotherapy with TMZ without adjuvant maintenance chemotherapy, Stupp regimen (cutoff of maximum of six courses)], complications of oncological treatments, and adverse events using WHO toxicity scale to grade the severity, oncological treatments at progression stages (such as: none, surgical resection with or without carmustine wafers implantation, chemotherapy (TMZ, other), radiotherapy, antiangiogenic therapy with Bevacizumab).

**Study endpoints**

The primary endpoint was OS, measured from the date of histopathological diagnosis after first surgical resection to the date of death. This interval was censored from the date of last follow-up for survivors. The secondary endpoint was PFS that was measured from the date of histopathological diagnosis to the date of first radiological evidence of progression according to MacDonald’s criteria or to the date of death. This interval was censored at the date of last follow-up for survivors.

**Statistical analysis**

Statistical analyses were performed using JMP software, version 11.0.0 (SAS Institute, Cary, NC, USA). Results are reported as mean ± standard deviation (SD) and range for continuous data. Categorical data are reported as percentages. A significance level of p < 0.05 was used. Comparisons among groups were performed using the chi-square or Fisher’s exact tests for comparing categorical variables, and the unpaired t-test or Mann–Whitney rank-sum test for comparing continuous variables, as appropriate. Associations between variables were determined using non-parametric Spearman’s rank order correlation. Kaplan–Meier analysis was performed for unadjusted survival curves, using log-rank tests to assess significance. Cox proportional hazards models were also constructed, adjusted for predictors associated with mortality or tumor progression in univariate analyses. Variables associated at the p < 0.2 level in unadjusted analysis were then entered into models, with the final model retaining only the variables significant at the p < 0.05 level.

**Results**

**Patients and tumors characteristics**

Eighty-three patients (50 men, 33 women) met the study inclusion criteria. Clinical, imaging, and surgical findings are summarized in Table I. The mean age at surgery was 59.9 ± 10.0 years (range, 21–78). Presenting symptom comprised neurological deficit in 62 cases (74.7%), intracranial hypertension in 31 cases (37.4%) and seizures in 15 cases (18.1%). Pleomorphic cell GBM was the most frequent histopathological subtype (n = 79, 95.2%), giant cell glioblastoma, and gliosarcoma were diagnosed in two and two cases, respectively.
The mean contrast-enhanced tumor volume at first surgery was 45.4 ± 30.2 cm$^3$ (range, 0.16–170.4). Postoperative contrast-enhanced imaging control included MRI in 64 cases (77.1%) and CT-scan in 15 cases (18.1%). We restricted the quantitative analysis of the extent of resection for cases with available preoperative and postoperative digitized contrast-enhanced MRI (n = 57): a total surgical removal was obtained in 28 cases (49.1%), a subtotal resection (78–99% of initial tumor volume) was obtained in 20 cases (35.1%), and a partial resection (<78%) was obtained in 9 cases (15.8%).

A mean 7.1 ± 1.7 (range, 3–13) carmustine wafers were implanted per surgery. There was a positive correlation between the preoperative contrast-enhanced tumor volume and the number of implanted carmustine wafers (r = 0.388, p < 0.001), the number of implanted carmustine wafers increasing with the tumor volume. There was no significant correlation between the extent of surgical resection or the percentage of surgical resection and the number of implanted carmustine wafers (r = 0.228, p = 0.131 and r = 0.006, p = 0.967, respectively).

**Surgical outcomes**

Thirteen patients (15.7%) developed a total of 16 adverse postoperative events (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/02688697.2015.1012051). Four patients (4.8%) had bacterial infectious surgical site complications (two abscesses, three meningitis), one of whom (1.2%) died 2.5 months after surgery. One patient (1.2%) had postoperative hematoma requiring surgical evacuation. In addition, a worsening of the neurological condition was observed in eight patients (9.6%) with four of these patients (4.8%) also developing nonsurgical adverse postoperative events (pneumonia, pyelonephritis, pulmonary embolism, acute pulmonary edema).

There was no significant association between the number of implanted carmustine wafers and the overall likelihood to adverse postoperative events (p = 0.599), overall surgical complications (p = 0.468), infectious surgical site complications (p = 0.896), or worsening of a patient’s neurological condition (p = 0.908).

**Postoperative oncological treatments**

**First-line oncological treatments**

Postoperative first-line oncological treatments were started in 80 cases (96.4%) (Table II). Radiation therapy was started in 79 cases (95.2%) at a mean 6.3 ± 1.7 weeks (range, 3–16) after surgery. The radiation therapy had to be discontinued in one case (1.3%). The first-line chemotherapy was TMZ in all cases. A Stupp regimen was administered in 61 cases (73.5%). Twenty-two patients did not receive a Stupp regimen: eight patients were treated before the Stupp era, in twelve cases based on a decision of a corresponding oncological center (1 case for altered postoperative performance status, 6 cases for age over 70, 5 cases for other causes), and two cases for...
postoperative complications precluding further oncological treatment (cases 2 and 3). The mean number of courses of adjuvant TMZ was 5.7 ± 3.6 (range, 1–27) with 28 patients (45.9%) having six or more courses of TMZ and seven of them (11.5%) having nine or more courses of adjuvant TMZ.

**Treatments at progression**

Sixty-nine first progressions (83.1%) were observed and new oncological treatments were started in 47 (68.1%) of those cases (Table II). A second surgery was performed in six cases (8.7%) with carmustine wafers implantation in four of these cases. Three patients had re-irradiation (4.3%). A systemic chemotherapy was administered in 44 patients (63.8%). Thirty-six secondary progressions (43.4%) were observed and new oncological treatments were started in 25 (69.4%) cases (Table II). A third surgical removal was performed in one case (2.8%) without carmustine wafers implantation and followed by systemic chemotherapy. A systemic chemotherapy was performed in the remaining 24 patients (96%).

**Adverse events during oncological treatments**

During first-line oncological treatment, 21 patients (26.6% of 79 patients that started radiotherapy) experienced 28 adverse events during and after radiotherapy (Supplementary Table II to be found online at http://informahealthcare.com/doi/abs/10.3109/02688697.2015.1012051). During adjuvant chemotherapy, 27 patients (50% of 54 patients that started adjuvant chemotherapy) experienced 31 adverse events.

**Survival analyses**

The mean follow-up period was 16.2 ± 9.7 months after histopathological diagnosis (median, 15.7; range, 2–53).

**Progression-free survival**

During the follow-up period first progressions were observed at a mean of 9.5 ± 6.9 months (median, 7.5; range, 2–41). At 1-year- and 2-years follow-up, 23.5% and 2.9% of patients were free of tumor progression, respectively (Fig. 1A).

Whatever the number of implanted carmustine wafers, the median PFS tended to be longer in the subgroup of patients with a subtotal and total surgical resection (9.5 months; mean, 10.0 ± 0.9) than in patients with a partial surgical resection (5.5 months; mean, 7.9 ± 1.2), without reaching statistical significance (p = 0.278). The median PFS was significantly longer in patients who had eight or more implanted carmustine wafers (8.5 months; mean, 10.7 ± 1.2) than in patients who had seven or less implanted carmustine wafers (5.0 months; mean 7.4 ± 1.0; p = 0.037) (Fig. 1B). The median PFS was significantly longer in patients treated with the Stupp regimen (8.5 months; mean, 10.6 ± 1.1) than in patients treated with any other type of postoperative treatments (4.7 months; mean, 6.8 ± 1.0; p = 0.020) (Fig. 1C). The median PFS was significantly longer in patients who had a maximal treatment (including subtotal and total resection plus eight or more implanted carmustine wafers plus a Stupp regimen with six or more courses of adjuvant TMZ) (12 months; mean, 13.8 ± 1.3) than in patients who had one or two of these therapeutic modalities (7.0 months; mean, 8.8 ± 0.9) or in patients who had none of these therapeutic modalities (4.7; mean, 4.8 ± 0.7; p < 0.001).

**Overall survival**

During the follow-up period, 56 patients (67.5%) died of tumor progression at a mean of 20.6 ± 1.7 months (median, 15.8; range, 2–53) since histopathological diagnosis. At second and third year follow-ups, 36% and 9.9% of patients were alive, respectively (Fig. 1A).

Whatever the number of implanted carmustine wafers, the median OS was significantly longer in patients who had a subtotal or total surgical resection (21.5 months; mean, 21.7 ± 1.7) than in patients who had only a partial surgical resection (13 months; mean, 12.9 ± 2.5; p = 0.011). The median OS was significantly longer in patients who had eight or more implanted carmustine wafers (24.5 months; mean, 23.3 ± 2.3) than in patients who had seven or less implanted carmustine wafers (15 months; mean, 15.9 ± 1.8; p = 0.021) (Fig. 1B). The median OS was significantly longer in patients who had a Stupp regimen (19.5 months; mean, 23.5 ± 2.2) than in patients who had any other type of postoperative treatments (13 months; mean, 13.6 ± 1.8; p = 0.002) (Fig. 1C). In the subgroup of patients who had a Stupp regimen (n = 61), the median OS was significantly longer in patients who had six or more courses of adjuvant TMZ (n = 28; 27 months; mean, 30.5 ± 3.5) than in patients who had less than six courses of adjuvant TMZ (n = 33; 16 months; mean, 15.5 ± 1.8; p < 0.001) (Fig. 1D). The median OS was significantly longer in patients who had a maximal treatment (including subtotal and total resection plus eight or more implanted carmustine wafers plus a Stupp regimen with six or more courses of adjuvant TMZ) (27 months; mean, 26.8 ± 1.9) than in patients who had one or two of these therapeutic modalities (18.5 months; mean, 19.5 ± 1.9) or in patients who had none of these therapeutic modalities (11.5 months; mean, 10.9 ± 1.6; p < 0.001).

**Predictors**

In univariate analysis (Table III), neurological deficit (p = 0.022), number of carmustine wafers (p = 0.037), and Stupp regimen (p = 0.020) were predictors of PFS. Tumor volume (p = 0.043), extent of surgical resection (p = 0.011), number of carmustine wafers (p = 0.021), and Stupp regimen (p = 0.002) were predictors of OS. In multivariate analysis (Table IV), independent prognostic factor for PFS was the presence of a neurological deficit (p = 0.022). Independent prognostic factors for OS were tumor volume (p = 0.014) and extent of surgical resection (p = 0.018). Of note, the parameters “number of implanted carmustine wafers” and “Stupp regimen” were statistically linked: the number of implanted carmustine wafers was significantly higher in the subgroup of patients who had a Stupp regimen (mean, 7.3 ± 1.5; range, 4–13; 67.2% with eight or more carmustine wafers) than in the subgroup of patients who had any other type of postoperative treatments (mean, 6.5 ± 2.0; range, 3–12; 40.9% with eight or more carmustine wafers) (p = 0.029).

To avoid the potential bias of Stupp regimen in the assessment of the prognostic significance of the number of implanted carmustine, we conducted a multivariate analysis in the subgroup of patients who had a Stupp regimen (n = 61). Independent
prognostic factors for OS were tumor volume \( (p = 0.003) \), extent of surgical resection \( (p = 0.005) \), and number of carmustine wafers \( (p = 0.008) \) (Table IV).

**Discussion**

Together with TMZ and Bevacizumab, carmustine wafers is one of the only three drugs approved by FDA for treatment of high-grade gliomas during the past decades. It was approved in 1996 and in 2003 for use in recurrent GBM and in newly diagnosed high-grade gliomas, respectively. This approval arose from two phase III trials, where the postoperative treatment consisted of external radiotherapy. Only few retrospective and prospective studies have previously analyzed the impact of the combination of carmustine wafers implantation together with the Stupp regimen for the treatment of newly diagnosed primary GBM. They have reported interesting results.
Carmustine wafers for glioblastomas

18 months for all patients and a median OS at 19.5 months in the subgroup of 61 patients that received a Stupp regimen, and a 4.8% rate of postoperative infectious complications. Several teams reported similar outcomes regarding this multimodal treatment. Interestingly, even if the study by the present study reports a single institution’s experience of intraoperative carmustine wafers either alone or in combination with the Stupp regimen for newly diagnosed primary GBM in 83 patients, paying close attention to patient survival and complication rates. We report a median OS at 18 months for all patients and a median OS at 19.5 months in the subgroup of 61 patients that received a Stupp regimen, and a 4.8% rate of postoperative infectious complications. Several teams reported similar outcomes regarding this multimodal treatment. Interestingly, even if the study by

Table III. Survival univariate analyses.

| Parameters                      | Overall survival | Progression-free survival |
|---------------------------------|------------------|---------------------------|
|                                 | Unadjusted       | Unadjusted                |
|                                 | Hazard Ratio     | Hazard Ratio              |
|                                 | CI 95% | p-value | HR CI 95% | p-value |
| Clinical parameters              |                 |                          |
| Gender                           |                 |                          |
| Female                           | 18.0 1 (ref)     |                          |
| Male                             | 16.5 1.14 0.66–2.00 0.646 | 7.5 1.04 0.64–1.74 0.887 |
| Age < 60                         | 17.5 1 (ref)     |                          |
| Age ≥ 60                         | 18.5 1.12 0.64–1.93 0.676 | 7.25 1.14 0.69–1.88 0.597 |
| Neurological deficit             |                 |                          |
| No                               | 16.5 1 (ref)     |                          |
| Yes                              | 17.9 0.93 0.52–1.78 0.819 | 5.3 2.02 1.12–3.51 0.022 |
| Karnofsky performance status     |                 |                          |
| > 70                             | 19.5 1 (ref)     |                          |
| ≥ 70                             | 16.0 1.12 0.59–2.01 0.719 | 7.0 1.01 0.57–1.68 0.979 |
| Imaging parameters               |                 |                          |
| Anatomic location                |                 |                          |
| Frontal                          | 15.0 1 (ref)     |                          |
| Temporal                         | 19.5 1.12 0.59–2.13 0.729 | 8.25 0.78 0.45–1.38 0.390 |
| Other                            | 18.0 1.01 0.48–2.09 0.973 | 8.5 1.03 0.32–1.24 0.281 |
| Ventricular contact              |                 |                          |
| No                               | 18.0 1 (ref)     |                          |
| Yes                              | 17.5 1.21 0.69–2.19 0.522 | 7.25 1.02 0.62–1.74 0.913 |
| Tumor volume, cm³                |                 |                          |
| < 40                             | 18.0 1 (ref)     |                          |
| ≥ 40                             | 16.0 1.88 1.02–3.52 0.043 | 7.0 1.06 0.63–1.78 0.836 |
| Therapeutic parameters           |                 |                          |
| Extent of resection              |                 |                          |
| Partial                         | 13.0 1 (ref)     |                          |
| subtotal and total               | 21.5 0.53 0.31–0.96 0.011 | 9.5 0.75 0.45–1.27 0.278 |
| Number of Carmustine wafers      |                 |                          |
| 7 and <                          | 13.0 1 (ref)     |                          |
| 8 and >                          | 24.5 0.56 0.32–0.96 0.021 | 8.5 0.59 0.36–0.99 0.037 |
| Stupp regimen                    |                 |                          |
| No                               | 13.0 1 (ref)     |                          |
| Yes                              | 19.5 0.42 0.24–0.75 0.002 | 8.5 0.51 0.30–0.89 0.020 |
| RPA classes                      |                 |                          |
| 3–4                              | 19.5 1 (ref)     |                          |
| 5–6                              | 10.5 1.64 0.77–3.15 0.188 | 6.5 1.39 0.72–2.49 0.308 |

CI, confidence interval; HR, hazard ratio

Table IV. Survival multivariate analyses.

| Parameters                      | Overall survival | Progression-free survival |
|---------------------------------|------------------|---------------------------|
|                                 | Unadjusted Hazard Ratio | Adjusted Hazard Ratio   |
|                                 | HR CI 95% | p-value | HR CI 95% | p-value |
| Clinical parameters              |                 |                          |
| Neurological deficit             |                 |                          |
| No                               | 1 (ref) 1.19–4.87 0.014 | 1 (ref) 1.12–3.88 0.022 |
| Yes                              | 2.38 1 (ref)     |                          |
| Imaging parameters               |                 |                          |
| Tumor volume, cm³                |                 |                          |
| < 40                             | 1 (ref) 1.19–4.87 0.014 | 1 (ref) 2.14 1.12–3.88 0.022 |
| ≥ 40                             | 3.38 1 (ref)     |                          |
| Therapeutic parameters           |                 |                          |
| Extent of resection              |                 |                          |
| Partial                         | 1 (ref) 0.25–0.88 0.018 | 1 (ref) 0.76 0.44–1.33 0.338 |
| subtotal and total               | 0.46 1 (ref)     |                          |
| Number of Carmustine wafers      |                 |                          |
| 7 and <                          | 1 (ref) 0.27–1.16 0.116 | 1 (ref) 0.46 0.29–1.01 0.055 |
| 8 and >                          | 0.68 0.34–1.42 0.303 | 0.46 0.29–1.01 0.055 |
| Stupp regimen                    |                 |                          |
| No                               | 1 (ref) 0.34–1.42 0.303 | 1 (ref) 0.46 0.29–1.01 0.055 |
| Yes                              | 0.68 1 (ref)     |                          |

CI, confidence interval; HR, hazard ratio
Noel et al. that combined grades III and IV tumors concluded that there was no significant influence of carmustine wafers on OS, one can observe that, in the GBM subgroup, the median OS was higher in cases with (20.8 months; n = 20) than without (13.8 months; n = 16) carmustine wafers implantation and that the difference was almost significant (p = 0.067). In line with previously published studies\textsuperscript{26,15} we confirm that the extent of surgical resection and the Stupp regimen are predictors of longer OS. We report for the first time the association between the number of implanted carmustine wafers and OS. In the literature, the reported number of implanted carmustine wafers has varied between one and nine and to date no association between patient survival and number of implanted wafers has been reported.\textsuperscript{9,17} In our study the number of implanted wafers varied between 3 and 13. Previous studies did not find a significant influence of the number of implanted carmustine wafers on OS but did report a significant increase in the risk of adverse events with the number of wafers implanted.\textsuperscript{28,11} Here, the OS and PFS were significantly longer in patients that had eight or more implanted carmustine wafers. We did not observe an increased risk of adverse events with a higher number of wafers implanted: the toxicity analyses confirm that the association of carmustine wafers implantation with the adjuvant therapies was well tolerated during first-line treatment of GBM. Particularly, the adverse events during adjuvant radiation therapy or conventional chemoradiotherapy were similar to those observed without carmustine wafers implantation. The positive correlation we observed between the number of implanted carmustine wafers and the tumor volume is explained by the large cavity performed by the removal of such tumor, whatever the extent of resection. The lack of correlation between the number of implanted carmustine wafers and the extent of resection is explained by the difficulty, in several cases, to ascertain intraoperatively the subtotal or total removal of the tumor. Indeed, some patients under study have had the carmustine wafers implantation in case of partial surgical resection. It was attributed to difficulties in intraoperative assessment of the extent of resection, when intraoperatively the neurosurgeon concluded to an “apparently gross total surgical removal”, while the postoperative MRI demonstrated a partial removal. As the NICE technology\textsuperscript{15} indicates the use of carmustine wafers only in case of surgical resection > 90%, the intraoperative implantation of carmustine wafers should be guided by surgical techniques such as fluorescence-guided resection with 5-aminolevulinic acid and intraoperative functional mapping that allow a maximal resection and a control of its extent.

We confirm that the tumor volume, the number of carmustine wafers, and the extent of resection were all independent prognostic factors for OS in the subgroup of patients who had a Stupp regimen. Thus, our findings of better outcomes in patients implanted with eight or more carmustine wafers and treated with the Stupp regimen regardless the extent of resection and initial tumor volume, strongly suggests that some patients could really benefit from this multimodal oncological treatment. The lack of MGMT methylation status precludes postoperative subgroup analyses, but the observed survivals in this unselected mixed population, including both MGMT-methylated and unmethylated patients, suggest an additional benefit from carmustine wafers implantation plus conventional chemoradiotherapy with TMZ.

Finally, the assessment of a multimodal oncological treatment combining intraoperative carmustine wafers together with the Stupp regimen for the first-line treatment of newly diagnosed primary GBM would benefit of a multicenter trial. The need of such a study, which should comprise molecular analyses, including the MGMT methylation status and the IDH mutation status,\textsuperscript{29,30} would help to identify the subgroups of patients that could benefit from such combination treatments and better characterize the modalities of use.

**Conclusion**

The intraoperative use of carmustine wafers in combination with Stupp regimen is a viable first-line treatment option of glioblastomas. The prognostic value of this treatment association should be evaluated in a multicenter trial, ideally in a randomized and placebo-controlled one.

**Acknowledgments**

These physicians are greatly acknowledged (in alphabetical order): Felipe Andreiuolo, Françoine Chassoux, Myriam Edjlali-Goujon, Anne Fustier, Sylvie Godon-Hardy, Maria Koziak, Elisabeth Landré, Michael Mann, Eric Méary, Charles Mellerio, Catherine Miquel, Olivier Naggara, Catherine Oppenheim, Céline Pallud, Matthew D. Potts, François-Xavier ROUX, Denis Trystram.

**Declaration of interest:** The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

**References**

1. Preusser M, de Ribaupierre S, Wohrer A, et al. Current concepts and management of glioblastoma. *Ann Neurol* 2011;70:9–21.
2. Pallud J, Dezamis E, Audureau E, et al. Neuronal immunoexpression and a distinct subtype of adult primary supratentorial glioblastoma with a better prognosis. *J Neurosurg* 2012;117:476–85.
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
4. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009;10:459–66.
5. Brem H, Plantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 1995;345:1008–12.
6. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003;5:79–88.
7. Duntze J, Litre CF, Eap C, et al. Implanted carmustine wafers followed by concomitant radiochemotherapy to treat newly diagnosed malignant gliomas: prospective, observational, multicenter study on 92 cases. *Ann Surg Oncol* 2013;20:2065–72.
8. Pan E, Mitchell SB, Tsai JS. A retrospective study of the safety of BCNU wafers with concurrent temozolomide and radiotherapy
and adjuvant temozolomide for newly diagnosed glioblastoma patients. *J Neurooncol* 2008;88:353–7.
9. Affronti ML, Heery CR, Herndon JE 2nd, et al. Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. *Cancer* 2009;115:3501–11.
10. Bock HC, Puchner MJ, Lohmann F, et al. First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience. *Neurosurg Rev* 2010;33:441–9.
11. McGirt MJ, Than KD, Weingart JD, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg* 2009;110:583–8.
12. Menel P, Metellus P, Parot-Schinkel E, et al. Biodegradable carmustine wafers (Gliadel) alone or in combination with chemoradiotherapy: the French experience. *Ann Surg Oncol* 2010;17:1740–6.
13. La Rocca R, Hodes I, Villanueva W, et al. (2006). A phase II study of radiation with concomitant and then sequential temozolomide (TMZ) in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine (BCNU) wafer insertion. Abstract presented at the Annual Meeting of the Society of Neuro-oncology, Orlando, FL (Abstract).
14. Salmaggi A, Milanesi I, Silvani A, et al. Prospective study of carmustine wafers in combination with 6-month metronomic temozolomide and radiation therapy in newly diagnosed glioblastoma: preliminary results. *J Neurosurg* 2013;118:821–9.
15. Barr JG, Grundy PL. The effects of the NICE Technology Appraisal 121 (gliadel and temozolomide) on survival in high-grade glioma. *Br J Neurosurg* 2012;26:818–22.
16. Louis DN, Ohgaki H, Wiestler OD, et al. *Glioblastoma multiforme*. Brain tumors of the central nervous system. *Acta Neuropathol* 2007;114:97–109.
17. Mirimanoff RO, Gorlia T, Mason W, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol* 2006;24:2563–9.
18. Berger MS, Tucker A, Spence A, Winn HR. Reoperation for glioma. *Clin Neurosurg* 1992;39:172–86.
19. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* 2011;115:3–8.
20. Cancer Therapy Evaluation Program (2006). Common terminology criteria for adverse events. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (Accessed 27 April 2013).
21. Vogelbaum MA, Jost S, Aghi MK, et al. Application of novel response/progression measures for surgically delivered therapies for gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group. *Neurosurgery* 2012;70:234–43.
22. Gallego JM, Barcia JA, Barcia-Mariño C. Fatal outcome related to carmustine implants in glioblastoma multiforme. *Acta Neurochir (Wien)* 2007;149:261–5.
23. Valtonen S, Timonen U, Toivanen P, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery* 1997;41:44–8.
24. Migliorini P, Bouchekova M, Rousseau B, et al. Impact of the per-operative application of GLIADEL wafers (BCNU, carmustine) in combination with temozolomide and radiotherapy in patients with glioblastoma multiforme: efficacy and toxicity. *Clin Neurol Neurosurg* 2012;114:1222–5.
25. Noël G, Schott R, Froelich S, et al. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior gliadel implantation (carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. *Int J Radiat Oncol Biol Phys* 2012;82:745–55.
26. McGirt MJ, Chiachana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg* 2009;110:156–62.
27. Darlix A, Baumann C, Lorgis V, et al. Prolonged administration of adjuvant temozolomide improves survival in adult patients with glioblastoma. *Anticancer Res* 2013;33:3467–74.
28. De Bonis P, Anile C, Pompacci A, et al. Safety and efficacy of Gliadel wafers for newly diagnosed and recurrent glioblastoma. *Acta Neurochir (Wien)* 2012;154:1371–8.
29. Metellus P, Coulibaly B, Nanni I, et al. Prognostic impact of O6-methylguanine-DNA methyltransferase silencing in patients with recurrent glioblastoma multiforme who undergo surgery and carmustine wafer implantation: a prospective patient cohort. *Cancer* 2009;115:4783–94.
30. Lechapt-Zalcman E, Levallet G, Dugué AE, et al. O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation and low MGMT-encoded protein expression as prognostic markers in glioblastoma patients treated with biodegradable carmustine wafer implants after initial surgery followed by radiotherapy with concomitant and adjuvant temozolomide. *Cancer* 2012;118:4545–54.

**Supplementary materials available online**

Supplemental Tables I and II.