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Sabel M

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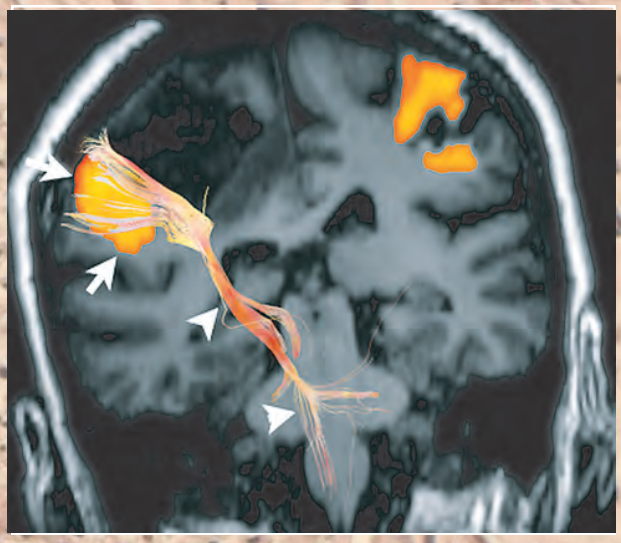

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Gliadel Wafers in Clinical Practice: The Neurosurgical View

Maria Angela Samis Zella*, Marion Rapp*, Hans Jakob Steiger, Michael Sabel

Abstract: Gliadel wafers are the only local chemotherapeutic agent approved for the treatment of primary and recurrent malignant gliomas. Since the approval, considerable clinical experiences in multimodal regimens have been made and require a re-evaluation from a neurosurgical point of view.

We reviewed the database entries from Medline, EMBASE, and BIOSIS from 2005–2012. Search terms included: gliadel, carmustine, or BCNU wafer, implant and complications or adverse events (AE).

Endpoints of our analysis were efficacy and safety data of gliadel for primary and recurrent glioblastomas. AEs included intracranial infections, oedema, healing abnormalities, CSF fistulae, and hydrocephalus.

For primary glioblastomas (GBM), median progression-free survival (PFS) reached 12.3 months and overall survival (OAS) ranged from 19.2–20.7 months. For recurrences, the 6-month OAS was 82 %, 1- and 2-year OAS rates were 47 % and 10 %, respectively. Median OAS was 50.3 weeks. AE rates for primary GBMs ranged from 0.8–16.7 % for cerebral oedema, from 4.4–8.3 % for healing abnormalities, 5.5 % for liquor leaks, from 0.0–47.0 % for hydrocephalus, and 4.8 % for intracranial infection. AE rates for recurrent glioblastomas ranged from 0.0–7.2 % for cerebral oedema, from 4.8–55.6 % for healing abnormalities, from 4.8–33.3 % for CSF fistulae, from 0.6–22.2 % for hydrocephalus and 5.0 % for intracranial infection.

The use of gliadel wafers is determined by the individual decision of the responsible neurosurgeon due to the absence of general guidelines. The AE rates reported in current treatment strategies are relatively low. **EANO Mag 2012; 2 (3): 129–32.**

Key words: high-grade glioma, glioblastoma, gliadel wafer, adverse events

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive form of malignant glioma, with an annual incidence of approximately 2–3 cases per 100,000 persons (CBTRUS, http://www.cbtrus.org) [1].

Since 2005, standard treatment for GBM consists of the largest possible, functionality-preserving surgical resection, followed by radiotherapy with concomitant chemotherapy with temozolomide (TMZ), followed by 6 cycles of TMZ [2]. Despite these important improvements in surgical and adjuvant therapy, GBM remains an incurable tumour. Median time to progression is 7 months and survival remains limited with about half of patients succumbing to the disease within 1–2 years after diagnosis [2, 3].

Strategies to improve outcome are therefore needed. An obvious approach is to consider the combination of all available treatment options. The carmustine wafer (Gliadel®) is a nitrosourea oncolytic agent consisting of 192.3 mg of a biodegradable polyanhydride copolymer and 7.7 mg of carmustine (1,3-bis (2-chloroethyl) -1-nitrosurea [BCNU]). Following surgical resection, these wafers are applied directly into the tumour cavity. The carmustine release takes place in a controlled manner over a period of 20 days and reaches high concentrations in peritumoural regions by diffusion.

In 2 phase-III studies [4, 5], Gliadel® was shown to prolong survival of GBM patients, yet many neurosurgeons are reluctant to use this treatment modality mostly because of the expected post-operative complications. This review provides a summary (unfortunately without formal statistical analysis) of the current literature, suggesting potential benefit of Gliadel® with reasonable toxicity and side effects. Such an overview points out the potential benefit of Gliadel®, and may help establish Gliadel® as part of the standard of care for patients with HGG. Therefore, it might be useful to review the current data on the impact of Gliadel© wafer implantation from a neurosurgical point of view.

Material and Methods

We performed a review of the available database entries from Medline, EMBASE, and BIOSIS from 2005–2012. Search terms included: Gliadel®, carmustine, or BCNU wafer, implant and complications or adverse events (AE). Results were limited to human studies and the use of BCNU wafers in patients with high-grade gliomas (HGG).

Endpoints of our analysis were the efficacy and the safety data of Gliadel® by primary and recurrent GBMs. We specifically screened for AEs previously described in phase-III studies [5] including intracranial infections, oedema, healing abnormalities, CSF fistulae, and hydrocephalus.

To estimate the overall incidence of AEs, rates of AEs from singular studies were summarized as median rates. Due to the heterogeneity of the studies included, we did not conduct a formal statistical analysis to determine comparability among groups. To underline consistent similarities or differences between groups concerning overall incidence and the median rate, we performed a qualitative comparison.

Pivotal Trials

Brem et al [4] demonstrated in a double-blinded, randomized, placebo-controlled study a significant survival benefit for recurrent GBM patients after Gliadel® implantation (median overall survival [OAS] of 7.2 months for BCNU wafer-treated

* Equally contributing authors

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From the Department of Neurosurgery, Heinrich Heine University Düsseldorf, Germany

Correspondence to: Maria Angela Samis Zella, MD, Department of Neurosurgery, Heinrich Heine University Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany; e-mail: samis.zella@med.uni-duesseldorf.de

patients vs 5.4 months for placebo wafer-treated patients). This study led to the approval of Gliadel® in the treatment of recurrent GBM in 1995.

For primary GBMs, a meta-analysis combining the results of the randomized phase-III trial published by Westphal et al [5] and a randomized phase-III study by Valtonen et al [6] demonstrated a survival increase to 13.1 vs 10.9 months for placebo patients (p = 0.03). The combined results of these trials led to regulatory approval of BCNU wafers for the treatment of newly diagnosed malignant gliomas in March 2003.

In 2005, Stupp et al [2] demonstrated the efficacy of radiation therapy and concomitant TMZ in newly diagnosed GBMs in a phase-III trial. This protocol marked in a revealing way the therapeutic path of GBMs patients and became the standard treatment for newly diagnosed GBMs. Therefore, data on the efficacy and complication rate of Gliadel® wafer implantation in primary and recurrent GBM patients treated with the Stupp protocol are now of great interest.

Efficacy of Gliadel® Wafer Implantation in Primary GBM in Combination with the Stupp Protocol

Although the combination of Gliadel® wafer implantation and concomitant radiochemotherapy with temozolomide might combine successful treatment strategies for malignant gliomas, combined treatment with the Stupp protocol and Gliadel® wafer implantation has been evaluated only in few retrospective studies.

In a retrospective, non-randomized study, De Bonis [7] analysed 165 patients with newly diagnosed (n = 77) or recurrent (n = 88) GBM for safety and efficacy of Gliadel® wafers. Multivariate analysis showed that the only factor associated with longer survival for newly diagnosed GBM was the extent of resection. Patients with a higher number of wafers implanted were significantly at risk for AEs. He concluded that adding Gliadel® to standard treatment did not significantly improve outcome, with a significant higher risk for toxicity after Gliadel® use.

By contrast, Miglierini [8] concluded that the concomitant use of surgery with implantation of BCNU wafers followed by radiochemotherapy according to the Stupp protocol seems to be well-tolerated. From 2006–2010, this retrospective single-centre study enrolled 24 newly diagnosed GBM patients and revealed a median OAS of 19.2 months. Median progression-free survival was 12.3 months in this cohort. McGirt et al [9] demonstrated a median OAS of 20.7 months after treatment with a combination of Gliadel® wafers and the Stupp protocol with acceptable side effects.

Continuative studies of 111 GBM patients treated initially with Gliadel® wafers followed by the Stupp protocol demonstrated that MGMT promoter methylation status and low MGMT expression both were identified as positive prognosticators [10].

As becomes evident from the analysis proposed, a lot of authors assert that the combination of Gliadel® wafer implantation and Stupp protocol may be a good strategy against GBM, but data available do not permit to suggest it as standard treatment.

Efficacy of Gliadel® Wafer Implantation in Recurrent GBM

After failure of the first-line therapy, the application of Gliadel® wafers for the treatment of recurrent GBM is still controversial.

Quinn [11] conducted a phase-II, open-label, single-centre trial on patients with recurrent GBM. After gross total resection of the tumour, up to 8 Gliadel® wafers were implanted. Bolus infusion of 06-benzylguanine (06-BG) was administered at 120 mg/m^2 over 1 hour on days 1, 3, and 5, along with a continuous infusion at 30 mg/m^2/d. 52 patients were accrued. The 6-month OS was 82 % (95-% confidence interval [95-% CI]: 72–93 %). The 1- and 2-year OS rates were 47 % (95-% CI: 35–63 %) and 10 % (95-% CI: 3–32 %), respectively. Median OS was 50.3 weeks (95-% CI: 36.1–69.4 weeks). Treatment-related toxicity with this drug combination included grade-3 hydrocephalus (9.6 %), grade-3 cerebrospinal fluid (CSF) leak (19.2 %), and grade-3 CSF/brain infection (13.4 %). The author simply concluded that more trials are required to verify that Gliadel® wafer implantation results in increased survival benefits without added toxicity.

Menei [12] reports the results of a retrospective multicentre study including 80 patients with a recurrent glioma; 58 of them received Gliadel® wafers as a second-line therapy and 22 as a first-line therapy. In this group, 20 % received conventional radiotherapy, 32.5 % received systemic chemotherapy, and 16.3 % received concomitant radiochemotherapy with TMZ according to the Stupp protocol. Median survival in the recurrent glioma group was 7 months. Total or subtotal excision appeared to have an important impact on survival (243 vs 122 days, 62 % reduction for risk of death, 95-% CI: 27–80 %; p = 0.002), as did preoperative KPS (253 vs 183 days, 56 % reduction for risk of death, 95-% CI: 15–77 %; p = 0.012) on univariate analysis.

In this analysis, Menei concluded that the combination of Gliadel® and radiochemotherapy with TMZ was well-tolerated and appeared to increase survival without increasing AEs.

De Bonis [7] analysed in the previously mentioned retrospective, non-randomized study survival data for 88 patients with recurrent GBM. He demonstrated that the only factor associated with a longer survival was the extent of resection and he concluded that adding Gliadel® to standard treatment did not significantly improve the outcome and that toxicity after Gliadel® use is significantly higher, both for patients with newly diagnosed and patients with recurrent GBM.

Efficacy data concerning recurrences are affected by a variety of factors and are still too controversial to tread a path regarding the better therapeutic strategies.

Surgical Complications of Gliadel® Wafer Implantation in Primary and Recurrent GBMs (Table 1)

Intracranial Infections

In both trial groups involving patients with newly diagnosed and recurrent GBMs, rates of AEs were similar.

The overall incidence of serious intracranial infections (abscesses, meningitis) has been shown to be equal in the recurrent group (5.0 %) and in the newly diagnosed GBM group (4.8 %), although without statistical significance. Attenello [13] retrospectively reviewed 1013 patients undergoing craniotomy for resection of malignant brain astrocytoma (World Health Organization grade-III/IV disease); a total of 288 (28 %) received Gliadel® wafers (250 glioblastoma multiforme [GBM], 38 anaplastic astrocytoma/anaplastic oligodendroglioma [AA/AO], 166 primary resection, 122 revision resection). He reported a rate of perioperative surgical site infection of 2.8 % among the Gliadel® population vs 1.8 % among the non-Gliadel® population (p = 0.33), for meningitis of 0.3 % among the Gliadel® population vs 0.3 % among the non-Gliadel® population (p = 1.00).

This data is in line with the literature considering patients with brain tumour undergoing craniotomy (0.1–43 %) [14].

Hydrocephalus

Similar results were observed considering the incidence of hydrocephalus requiring a VPS; the range was 0.0–47.0 % of the patients with newly diagnosed GBMs versus 0.6%–22.2% of patients with recurrences. A recent study specifically designed to analyze the incidence of adverse events in first-line treatment of malignant glioma reported a postoperative hydrocephalus at an incidence of 7 % [15].

These studies confirmed the elevated risk of hydrocephalus associated with Gliadel® wafer implantation. Other studies indicate, however, that the risk of a hydrocephalus requiring an operative treatment does not appear to be increased with the use of Gliadel® wafers [15].

CSF Fistulae

According to the pivotal trials the incidence of CSF fistulae appears more common in the Gliadel® wafer group than in the placebo wafer group (5 vs 0.8 %), but this difference did not reach statistical significance.

Between the patients with newly diagnosed GBMs the risk of developing CSF fistulae reaches a median value of 5.5 % for newly diagnosed patients versus a risk ranging from 4.8–33.3 % for patients with recurrences (median value 9.1).

Attenello [13] reported a rate of CSF leak of 2.8 among the Gliadel® population versus 1.8 among the non-Gliadel® population (p = 0.33).

Gallego et al [16] reported 3 patients who had fatal hydrocephalus and CSF fistulae related to Gliadel® wafer implantation.

Healing Abnormalities

Pivotal trials showed a significant difference in the incidence of healing abnormalities: 14 % for the Gliadel® wafers group and 5 % for the placebo wafers group (p = 0.05). In non-phase-III trials, healing abnormalities appear to be one of the most common AEs [5] and appear to be higher in recurrent disease with a median value of 4.4 % than in newly diagnosed disease with a median value of 21.3 % [17–22].

According to the more recent literature, the rate of healing abnormalities is comprised in a range from 4.4–8.3 % of the patients with a newly diagnosed GBM and in a range from 4.8–55.6 % of the patients with recurrences [22]. Attenello [13] reported a rate of healing abnormalities of 0.7 among the Gliadel® population versus 0.4 among the non-Gliadel® population (p = 0.63).

Oedema

The trials considered did not underline any difference between the groups for brain oedema: the overall incidence in patients with newly diagnosed disease ranged from 0.8–16.7 % and from 0.0–7.2 % for recurrences. According to Attenello's retrospective study [13], a rate of oedema of 2.1 % among the Gliadel® population versus 2.3 % among the non-Gliadel® population (p = 1.00) was reached.

These data appear comparable to those registered by phase-III pivotal studies where patients who received Gliadel® wafers for recurrent HGGs reached a rate of 4 % of oedema [22].

In spite of the heterogeneity of the complication rates demonstrated in patients treated with Gliadel® wafers by the listed studies, one can infer that the complication rate is relatively low and, when present, these complications require minor treatment.

Conclusion and Future Aspects

Gliadel® wafers are approved for the treatment of patients with newly diagnosed GBMs as adjunct to surgery and radiation and are also indicated to treat recurrent GBMs. Their approval was based on clinical trial results showing the median survival of patients with high-grade malignant gliomas increased to 13.1 vs 10.9 months for placebo patients (p = 0.03) [5], and the median survival of patients with recurrent GBM increased from 5.4 months to 7.2 months [4].

Table 1. Rates of surgical complications following Gliadel® wafer implantation in primary and recurrent glioblastomas (GBM).

	Newly diagnosed GBM (%)	Recurrent GBM (%)
Hydrocephalus	0.0–47.0	0.6–22.2
CSF leak	5.5	4.8–33.3
CSF/Brain infections	4.8	5.0
Healing abnormalities	4.4–8.3	4.8–55.6
Oedema	0.8–16.7	0.0–7.2

Despite these results, the current data available on the use of Gliadel® wafers in primary or recurrent GBM are still controversial. First, since there are no prospective, randomized trials available on the efficacy and toxicity of Gliadel® wafer implantations after the introduction of the Stupp protocol, the use of Gliadel® wafers will be more determined by the individual decision of the responsible neurosurgeon than by general guidelines.

Second, since the complication rates for the implantation groups in most studies are consistent with the rates from historical BCNU wafer studies, the fear of complications should not preclude the use of BCNU wafers by recurrent GBMs after pre-treatment with the Stupp protocol. Survival data indicate a potential benefit, but formal, prospective studies are needed to more thoroughly assess toxicity risk and any potential survival benefit.

Both of these dichotomies need to be addressed for further studies, if possible, or for further progress to be realized.

Conflict of Interest

The authors state that no conflict of interest exists.

References:

1. Deorah S, Lynch CF, Sibenaller ZA, et al. Trends in brain cancer incidence and survival in the United States: Surveillance, Epidemiology, and End Results Program, 1973 to 2001. Neurosurg Focus 2006; 20: E1.

2. Stupp R, Mason WP, van den Bent MJ; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987–96.

3. Dixit S, Baker L, Walmsley V, et al. Temozolomide-related idiosyncratic and other uncommon toxicities: a systematic review. Anticancer Drugs 2012; 23: 1099–106.

4. Brem H, Piantadosi 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.

5. 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.

6. 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: 44–9.

7. De Bonis P, Anile C, Pompucci A, et al. Safety and efficacy of gliadel wafers for newly diagnosed and recurrent glioblastoma. Acta Neurochir (Wien) 2012; 154: 1371–8.

8. Miglierini P, Bouchekoua M, Rousseau B, et al. Impact of the per-operatory 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.

9. 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.

10. 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.

11. Quinn JA, Jiang SX, Carter J, et al. Phase II trial of gliadel plus O6-benzylguanine in adults with recurrent glioblastoma multiforme. Clin Cancer Res 2009; 15: 1064–8.

12. Menei P, Metellus P, Parot-Schinkel E, et al. Biodegradable carmustine wafers (gliadel) alone or in combination with chemotherapy: the French experience. Ann Surg Oncol 2010; 17: 1740–6.

13. Attenello FJ, Mukherjee D, Datoo G, et al. Use of gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. Ann Surg Oncol 2008; 15: 2887–93.

14. Rabadan AT, Hernandez D, Eleta M, et al. Factors related to surgical complications and their impact on the functional status in 236 open surgeries for malignant tumors in a Latino-American hospital. Surg Neurol 2007; 68: 412–20.

15. Bock HC, Puchner M, 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.

16. Gallego JM, Barcia JA, Barcia-Marino C. Fatal outcome related to carmustine implants in glioblastoma multiforme. Acta Neurochir 2007; 149: 261–5.

17. La Rocca R, Glisson S, Hargis J, et al. High-grade glioma treated with surgery; carmustine wafer; postoperative radiation; and procarbazine, lomustine, and vincristine chemotherapy. Neurosurg Q 2005; 15: 167–71.

18. 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.

19. Asher AL. Prospective analysis of temozolomide as adjuvant to gliadel and radiation in newly diagnosed malignant glioma. Abstract: Annual Meeting of the American Association of Neurological Surgeons, Washington, DC, 2007.

20. Uff CEG, Bradford R. Use of gliadel (BCNU) wafers in high grade glioma. Abstract: Meeting of the Society of British Neurosurgeons, Plymouth, UK, 2005.

21. Weingart J, Grossman SA, Carson KA, et al. Phase I trial of polifeprosan 20 with carmustine implant plus continuous infusion of intravenous O6-benzylguanine in adults with recurrent malignant glioma: new approaches to brain tumor therapy CNS consortium trial. J Clin Oncol 2007; 25: 399–404.

22. Sabel M, Giese A. Safety profile of carmustine wafers in malignant glioma: a review of controlled trials and a decade of clinical experience. Curr Med Res Opin 2008; 24: 3239–57.