Safety and efficacy of Gliadel wafers for newly diagnosed and recurrent glioblastomas

Domenico d'Avella • Alessandro DellaPuppa

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The paper by De Bonis and his colleagues from Rome in this issue of *Acta Neurochirurgica* is timely given the continuing controversy between standard versus a more aggressive attitude with newly diagnosed and recurrent glioblastomas. Gliadel® wafers are designed to release carmustine slowly over a period of 2–4 weeks after placement into the surgical cavity of high-grade glioma. This will result in high concentrations of carmustine locally elevated up to 100 fold over levels achieved with systemic delivery of biodegradable carmustine (BCNU). In 1995, Brem et al. [2] reported in *Lancet* on a phase III study of 222 patients with recurrent malignant glioma in which the median survival of the 110 patients who received carmustine polymers was 31 weeks compared with 23 weeks for the 112 patients who received only placebo polymers. There were no clinically important adverse reactions related to the carmustine polymer. In 2003, Westphal et al. [12] presented a phase III trial on 224 patients affected by newly diagnosed high-grade glioma that were randomized to receive either BCNU or placebo wafers at the time of primary surgical resection; both groups were treated with external beam radiation post-operatively. Median survival was 13.9 months for the BCNU wafer-treated group and 11.6 months for the placebo-treated group. Adverse events were comparable for the two groups, except for CSF leakage (5 % in the

BCNU wafer-treated group vs. 0.8 % in the placebo-treated group) and intracranial hypertension (9.1 % in the BCNU wafer-treated group vs. 1.7 % in the placebo group). In 2006, for the same cohort of patients, Westphal et al. [13] published in *Acta* a survival advantage at 2 and 3 years follow-up for Gliadel treatment compared with placebo. Up to now, a large quantity of non-phase III studies and local experiences have been published on both the safety and efficacy of Gliadel. However, one major current issue is the lack of consensus on the use of Gliadel implantation into the surgical cavity and concomitant temozolomide with radiotherapy followed by adjuvant temozolomide (the Stupp protocol). In the TA121 guideline [7], NICE (National Institute for Health and Clinical Excellence) could not express any opinion on the sequential use of either regimen because of the lack of evidence at the time of consultation. More recently, preliminary results of a phase II multicenter clinical trial and of retrospective series have reported an incremental gain of 2–3 months in median survival in comparison to the published results using Gliadel or the Stupp protocol alone. No increased complication rate with carmustine use was detected. However, at present, we are lacking a phase III study on this multimodal treatment.

De Bonis and colleagues retrospectively analyzed safety and efficacy data of 47 consecutive patients affected by newly diagnosed or recurrent glioblastoma who underwent multimodal treatment with implantation of Gliadel wafers in their department. They concluded that no difference in survival was observed for patients receiving Gliadel wafers and that the incidence of AEs reported in their study was comparable to that reported previously in the literature. As correctly stated by the authors, the design of the study presents some limitations. In fact, the retrospective nature of the analysis does not permit us to look at these data without some constraints. However, we would like to thank

D. d'Avella (✉)
University of Padova, Neurosciences,
via Giustiniani 5,
Padova 35128, Italy
e-mail: domenico.davella@unipd.it

A. DellaPuppa
Department of Neurosciences, Division of Neurosurgery Azienda,
Ospedaliera Università di Padova,
Padova, Italy

the authors because their paper interestingly focuses on a noteworthy issue for glioma patients treated with BCNU wafers, the safety data. Actually, in their experience both patients with a higher number of wafers implanted and patients with recurrent tumors were significantly at risk for adverse events (AE) and implantation site-related adverse events (ISAE). In addition, they pointed out the importance of postoperative follow-up in their experience to improve safety data. We think that this issue is important for these patients.

As a matter of fact, a recent NICE study [10] reported that only about one third of patients suitable for carmustine wafer therapy received them, revealing a wide variation in practice even in the same country. This could be related to the high cost of the treatment, which normally then has to be added to other adjuvant therapies. Another cause could be that BCNU wafer placement frequently represents an *exclusion criterion* for recruitment of patients into further clinical trials. However, we think that a possible role could be played by an imprecise fear of possible wafers-related adverse events.

At our department, we treated 81 patients with BCNU wafers in the last 4 years (about 20 % of the total HGG patients operated on at our department in the same period). Adverse events were detected in 21 % of patients (16 % in newly diagnosed and 23 % in recurrent glioma patients, respectively). All patients affected by a newly diagnosed high-grade glioma underwent the Stupp protocol. The median survival of newly diagnosed GBM patients was 22 months; overall survival at 2 and 3 years was 38 % and 18 %, respectively. Median survival of recurrent GBM patients was 11 months. We usually place BCNU wafers in patients who present a preoperative KFS score of 100; possible radical resection is a precondition. This policy should not be neglected when analyzing our efficacy data because a strict selection of patients certainly has a significant influence.

The lesson we learned at our department was that selection and follow-up of patients were both pivotal to prevent and to successfully treat adverse events. We completely agree with De Bonis and colleagues that safety data may improve over time with the increasing experience of the center.

We experienced a percentage reduction of patients affected by one or more adverse event from 40 % in 2007 to 8 % in 2011. This learning curve could explain the wide range of AE incidence between different centers reported in the literature [1]. In this sense, safety data could be better when surgery is performed in a high-volume center. For the same reason, we think that data from high-volume centers are probably what we should strictly pursue. In this regard, for example, we should always bear in mind the 10-year experience of Johns Hopkins; their paper is at present the largest reported cohort of Gliadel implantation [8].

In our experience, a correct intraoperative policy (careful dural closure, ventricular communication repair) [5], judicious perioperative management (corticosteroids, anti-epileptic and deep vein thrombosis prophylaxis) [4], and strict clinical and radiological postoperative follow-up [6] were crucial. In the postoperative stage, the early detection of cyst formation in the surgical cavity was important for patient management. In fact, in our experience, this finding was associated with one or more clinical symptoms in about 40 % of cases. Prolonged corticosteroid treatment was sufficient to control the transitory symptomatology related to cyst development. Our current policy of performing an MRI on these patients before discharge enables us to guide corticosteroid withdrawal over the first weeks after surgery in order to protect patients from symptoms. Familiarity with this phenomenon is in our opinion fundamental for the rational management of these patients; actually, in the past it was not infrequently misunderstood, and surgery was preferred to medical treatment to exclude septic complications or early tumor progression. Recently, some authors have confirmed this finding and interestingly reported it as an early pseudo-progression [3, 11].

As correctly reported by De Bonis and colleagues, stratification of patients is pivotal to analyze the safety and efficacy data of treatments rationally. With regard to this multimodal treatment, the interesting data recently published in *Cancer* [9] about the prognostic impact of MGMT in patients with newly diagnosed glioblastoma who receive carmustine-releasing wafers (Gliadel) along with temozolomide must be emphasized. Patients with tumors that harbored MGMT methylation had a significantly longer OS compared with patients who had wild-type MGMT (21.7 months vs. 15.1 months; $P=0.025$). Similarly, patients who had low MGMT protein expression (≤ 15 %) had a significantly improved OS compared with patients who had high MGMT expression (27.0 months vs. 15.1 months; $P=0.021$).

We would like to suggest two points that should be analyzed in more depth in this setting: first, the identification of subgroups of patients that could benefit from BCNU wafers more than temodal treatment. This could be the case when systemic chemotherapeutic exposure could be hazardous or the Stupp protocol could not be carried out entirely, for many reasons (older patients, for example). The second is to investigate the association of Gliadel with new molecules in the treatment of recurrent high-grade gliomas relapsing during temodal treatment.

Finally, when carmustine wafer placement is planned, we know that a main goal of surgery must be gross total resection of the tumor. With regard to this issue, we would like to point out our preliminary experience (11 cases) with patients affected by high-grade glioma treated with BCNU wafers in which surgical resection was guided by 5-aminolevulinic acid-based fluorescence. The combined use was feasible

and reliable. No adverse events referable to the association were detected. This is an emerging issue that should be investigated in the near future to improve even more the efficacy data on this treatment.

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Conflicts of interest None.

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