

The first 3 months after BCNU wafers implantation in high-grade glioma patients: clinical and radiological considerations on a clinical series

Alessandro Della Puppa · Marta Rossetto · Pietro Ciccarino · Giulia Del Moro ·
Antonino Rotilio · Renzo Manara · Marina Paola Gardiman · Luca Denaro ·
Domenico d'Avella · Renato Scienza

Received: 11 June 2010 / Accepted: 23 July 2010 / Published online: 13 August 2010
© Springer-Verlag 2010

Abstract

Purpose Carmustine (1,3-bis[2-chloroethyl]-1-nitrosurea (BCNU)) wafers are approved for the local treatment of newly diagnosed and recurrent malignant glioma. Reassuring data on both safety and efficacy of treatment have been previously reported by phase III studies. Although most of related adverse events are reported in the first few months after surgery, there is a lack in the literature of radiological data regarding this period. Few anecdotal experiences have been reported about surgical bed cyst occurrence. The aim of our study is to analyse the radiological course of patients treated with wafers implantation focusing on the relationship between radiological data, and in particular bed cyst occurrence, and safety data.

Methods Forty-three patients affected by malignant glioma underwent surgical removal and BCNU wafers implanta-

tion at the Department of Neurosurgery of Padova from April 2007 to October 2009. Safety data were collected according to previously reported phase III studies. Patients underwent clinical and radiological evaluation (MRI) postoperatively, then before discharge, at 1 month, then every 2 months. In the study were included only patients whose both 1- and 3-month MRIs were available. Finally, 36 out of 43 patients were available for the revision.

Findings Fifty-eight percent of patients treated with BCNU wafers presented a bed cyst of the surgical cave at the 1-month MRI. Forty-eight percent of them were symptomatic. Conversely, among patients who presented one or more adverse event (27%), bed cyst was detected in up to 90% of cases (OR 7.35), being intracranial hypertension more frequently associated (OR 7.35; p value <0.05). In general, cysts presented a benign behaviour in the sense that patients promptly improved with corticosteroid treatment, never required surgery, never reported permanent neurological deficits.

Conclusions Surgical bed cyst occurrence in BCNU wafer-treated patients resulted more frequent than expected. Familiarity with the event is important to correctly handle a possible evolving phenomenon. However, only further larger experiences and prospective studies could reveal how the understanding of such event might be helpful to improve safety data.

Keywords Carmustine wafers · Safety · Surgical bed cyst · High-grade gliomas

A. Della Puppa · M. Rossetto · P. Ciccarino · G. Del Moro ·
A. Rotilio · L. Denaro · R. Scienza
Neurosurgery, Department of Neurosciences,
Padova University Hospital,
Padova, Italy

R. Manara
Department of Neuro-Radiology, Padova University Hospital,
Padova, Italy

M. Paola Gardiman
Department of Pathology, Padova University Hospital,
Padova, Italy

D. d'Avella
Department of Neurosciences, Padova University Hospital,
Padova, Italy

D. d'Avella (✉)
Department of Neurosciences, University Hospital of Padova,
Via Giustiniani 2, Azienda Ospedaliera di Padova,
35128 Padova, Italy
e-mail: domenico.davella@unipd.it

Introduction

Carmustine (1,3-bis[2-chloroethyl]-1-nitrosurea (BCNU)) wafers are an approved treatment for newly diagnosed and

recurrent malignant glioma. Safety and efficacy of treatment have been established by phase III studies [3, 25]. Additional experiences have been subsequently published [1, 2, 4–6, 9–13, 15, 16, 18–22, 24]. More recently, a large mono-institutional experience on newly diagnosed GBM patients treated with Gliadel associated to radio-chemotherapy with Temozolomide reported a median survival of nearly 21.3 months and a 2-year survival rate of 39% [15]. Surgical bed cyst occurrence among patients operated on for a malignant glioma is well-known [23], and it is commonly considered likelier to present after BCNU wafers implantation. However, up to now, no large studies have been reported in literature focusing on the event in BCNU wafer-treated population. Most of the patients presenting with this new local mass with contrast-enhancing margins introduced a diagnostic problem so revision surgery was not infrequently performed in the clinical suspicion of tumour recurrence [7, 8, 12–14]. In addition, we have no data about clinical behaviour of bed cysts since the few reported cases were aggressively treated by surgery and corticosteroid therapy [7, 8, 13, 14, 23]. In our opinion, surgical bed cyst finding in the postoperative period of patients treated with BCNU wafers is an important issue because it may represent a diagnostic pitfall and be itself a possible evolving phenomenon. We present here our experience about the first postoperative 3 months on a consecutive series of 36 patients affected by high-grade glioma and treated with BCNU wafers. The revision was particularly focused on the description of bed cyst occurrence and its clinical presentation.

Materials and methods

Patient and tumours

We retrospectively reviewed 43 cases of craniotomy for resection and BCNU wafers implant of malignant brain astrocytoma (World Health Organization (WHO) grades 3 or 4) performed at Department of Neurosurgery of Padova from April 2007 to October 2009. All patients were operated on in a MRI neuro-navigational setting. Patients' presenting clinical, radiological, operative and hospital course records were retrospectively reviewed. Outpatient clinic notes were available from both neurosurgical and neuro-oncology follow-up visits and reviewed in all cases. Demographics, presenting symptoms and signs, Karnofsky performance score, peri-operative morbidity, intraoperative use of Gliadel were collected. Tumour grade was histologically confirmed in all cases. All patients underwent peri-operative antiepileptic and antibiotic prophylaxis. Corticosteroid treatment was dexametasone 16 mg/die during the first week and subsequently adjusted on the basis of clinical and radiolog-

ical findings. Patients whose 3-month follow-up was not available was recorded as lost to follow-up and not included in the study.

Patients and treatment

All patients (newly diagnosed and recurrent GBM) performed adjuvant treatment after surgery. Patients affected by newly diagnosed high-grade gliomas underwent radio and chemotherapeutical treatment. Within 6 weeks from surgery and BCNU wafers implantation, external beam radiation was administered at a dose of 1.8–2.0 Gy per day over 6 weeks, for a total dose of 59.4–60.0 Gy. Oral TMZ was administered concurrently with radiotherapy at a dose of 75 mg/m² daily for 6 weeks. One-month MRI was performed to have a radiological evaluation pre-adjuvant treatment. Within 2–4 weeks of completion of chemoradiotherapy, patients received TMZ at 200 mg/m² daily for 5 days during a 28-day cycle and for at least 6 cycles.

Patients affected by recurrent tumours did not undergo radiotherapy. In all cases within 6 weeks from surgery, alchylant-based chemotherapy was administered.

Inclusion and exclusion criteria

Inclusion criteria for our study were Carmustine wafers implantation after malignant glioma resection and available clinical and radiological follow-up data about first 3 months after surgery. In particular, only patients who performed both 1- and 3-month MRI were revised. According to these criteria, only 36 out of 43 patients were included in the study.

Implantation technique of BCNU wafers

BCNU wafers were not implanted when tumour was multifocal, when it extended across corpus callosum, when its resection required a large opening of the ventricle or when it was intra-operatively thought to be sub-totally resected. BCNU wafers were implanted after surgical removal of tumour and intra-operative pathological confirmation of high-grade glioma. When a little ventricular defect was obtained, the defect was repaired by means of a piece of sponge fixed with some fibrin glues. If the final result was a complete exclusion of ventricular cavities from surgical cave, up to eight BCNU wafers were then implanted.

Clinical follow-up

Patients were clinically evaluated pre-operatively, post-operatively, before discharge and then every month. In

any case, a neurological assessment was performed. In particular, according to phase III studies (3,26) patients were investigated for BCNU wafer-related adverse events such as signs of infection, wound healing abnormalities (CSF leak and skin abnormalities), intracranial hypertension symptoms (see “Research Variables”).

MRI sequences and follow-up

MRI was performed with 1.5-T GE scanner (Achieva, Philips, Best, The Netherlands). All MRI studies included Fluid Attenuated Inversion Recovery, T2-weighted and T1-weighted before and after administration of Gadolinium contrast material (gadopentetate dimeglumine). MRI was performed within 48 h from surgery to evaluate extent of removal. Degree of resection was retrospectively classified from postoperative MRIs as gross total resection (no residual nodular enhancement on MRI) or as subtotal resection (residual nodular enhancement on MRI). Since BCNU-treated patients were expected to present an adverse event related to BCNU wafers implant within the 3 months after surgery, they underwent subsequent MRI at 7 days (pre-discharge), 1 and 3 months after surgery. One-month MRI was performed also to assess patients’ status before beginning of other treatments. Then, patient performed MRI 3 months after surgery and then every 2 months. Pre- and postoperative MRI reports documented by an attending neuroradiologist were re-evaluated.

Research variables

The aim of the study was to analyse clinical data and radiological data within the first 3 months after BCNU wafers implantation. To compare our data to larger experiences’ data, safety data were recorded according to what was previously described by phase III studies and large revision studies [3, 19, 25]. The incidence of peri-operative morbidity was assessed during the first 3 months after surgery in all cases. Morbidities included peri-operative surgical site infection, CSF leak, meningitis, incisional wound healing difficulty, symptomatic malignant oedema, 3-month seizure incidence, deep-vein thrombosis, pulmonary embolism and hydrocephalus. Symptomatic malignant oedema was defined as an acute increase in oedema surrounding the resection cavity in the first 3 months that was not attributed to early tumour progression and that required hospital admission for corticosteroid therapy. Wound healing difficulty was defined as non-infectious dehiscence or wound breakdown occurring within the first 3 months after surgery. The incidence of 3-month seizure activity was defined by the presence of simple or generalised partial or complex seizure activity occurring within the first 3 months after surgery. Radiological investigations particularly pointed to evaluate bed cyst occurrence.

To adapt multiplicity of adverse events to radiological findings in the data analysis, patients affected by one or more adverse event related to BCNU wafers were defined as “symptomatic”; conversely, “asymptomatic” were defined patients who did not present any adverse event related to BCNU treatment. To evaluate possible risk factors for bed cyst formation, preoperative size of tumour (maximum diameter on T1-weighted MRI images after contrast administration) and site of cyst developing (cortical–sub-cortical junction vs. deep-seated lesion) were recorded. To evaluate if safety data could be correlated to cysts’ site, areas of cyst arising were distinct in eloquent and not eloquent. Eloquent were considered the areas involved in motor, speech, sensitive and visual functions. Finally, demographics, Karnofsky performance score and intra-operative use of Carmustine wafers were also recorded.

Statistical methods

Parametric data were expressed as mean $\pm$ standard deviation (SD). Non-parametric data were expressed as median (interquartile range). Count data (categorical variables) were compared between cohorts via χ^2 test in two-way tables. If any value was <10 in the two-way table, Fisher’s exact test was used.

Ethical approvals

An informed consent concerning treatment and postoperative follow-up was signed by all patients.

Results

Patient population

Thirty-six patients were included in the study (Table 1). Twenty-four patients (67%) were men and 12 were women

Table 1 Clinical characteristics of patients

Variable	All patients (<i>n</i> =43)	Reviewed (<i>n</i> =36)
Age (year), mean $\pm$ DS	54 $\pm$ 12	55 $\pm$ 11
Male sex	27 (63%)	24 (67%)
Karnofsky performance status, median [IQR]	100 [90,100]	100 [90,100]
Preoperative seizures	5 (11%)	4 (11%)
Revision resection	23 (53.5%)	18 (50%)
Gross total resection	30 (70%)	20 (56%)
<i>n</i> Wafer implanted, median [IQR]	8 [4, 8]	8 [4, 8]

(33%). Mean age was 56 (± 12 SD). Median preoperative KFS score of patients was 100 [90–100]. Eighteen patients (50%) underwent primary resection and subsequent radio-treatment. Eighteen patients (50%) underwent revision resection while no radio-treatment was performed. Twenty patients (56%) received gross total resection of tumour, and 16 (44%) received subtotal resection. Histopathological report was of astrocytoma grade IV section WHO in 33 patients (91.7%) and astrocytoma grade III section WHO in three patients (8.3%). Median number of wafers implanted was eight [range 4–8].

Peri-operative morbidity

Peri-operative morbidities of the 36 patients included in the study are summarised in Table 2. Ten (27.8%) presented at least one adverse event in the postoperative course (“symptomatic patients”). Discrepancy between the sum of total adverse events’ incidence and the number of patients affected is due to the coexistence in some patients of multiple complications. Indeed, nine of them had multiple adverse events. Three patients (8%) experienced postoperative seizures; among them two within the first week after surgery. Surgical site infection was observed in one patient (2.8%) after removal of a recurrent glioma. Deep-vein thrombosis was observed in three patients (8%). None of our patients had pulmonary embolism. Healing abnormalities were found in three patients (8%) while CSF leaks in two (5.5%). One patient had symptomatic cerebral oedema requiring re-admission for e.v. high-dose corticosteroid administration. All patients who developed an adverse event were also affected by intracranial hypertension related symptoms: six of them had been treated for a newly diagnosed glioma and four of them for a recurrent

glioma. Among patients who presented an adverse event, 50% underwent a gross total tumour resection while 50% underwent a subtotal resection.

Radiological findings

Undergoing 1-month MRI, 21 patients (58%) showed a surgical bed cyst (Table 3). In all cases, it appeared decreased in volume at the 3-month MRI. This was the case of both radio-treated patients and not radio-treated patients. Thirteen of them (62%) had a subtotal tumour removal. Cyst incidence in patients treated for a newly diagnosed malignant glioma (radio-treated group) was 57%, and in recurrent malignant glioma-treated patients, it was 43%, showing no statistically significant differences ($p=1.05$). Cysts developed equally in grade IV and in grade III tumour. Among patients with bed cyst detection at 1-month MRI, 43% presented one or more adverse event while 57% were asymptomatic. Conversely, among patients with no bed cyst detection at 1-month MRI, 7% presented one or more adverse event while 93% were asymptomatic. However, among patients with one or more adverse event 90% presented bed cyst of the surgical cave. In all cases, bed cyst were associated to raised intracranial pressure symptoms. Bed cysts formation had analogous incidence both in large (≥ 3 cm) and in small tumours (< 3 cm). There was no statistically significant association between cyst formation and tumour location (cortical–sub-cortical junction vs. deep-seated lesion). However, symptomatic cysts appeared to develop more frequently when the original tumour major diameter was ≥ 3 cm, and all of them were in eloquent areas.

Discussion

Our present relevant results

Table 2 Peri-operative morbidities of the 36 patients included in the study

Adverse event	Patients (n)	Percentage (n=36)
Cerebral oedema	5	13.8
Malignant symptomatic cerebral oedema	1	2.8
Intracranial hypertension	10	27.8
Healing abnormalities	3	8.3
CSF leaks	2	5.5
Intracranial infections	1	2.8
Seizures	3	8.3
Thromboembolic events	3	8.3
Deep vein thrombosis	3	8.3
Pulmonary embolus	0	0
Hydrocephalus	0	0

Safety data have been summarised in Table 2. Intracranial hypertension represented the more frequent adverse event (27%) while seizures, healing abnormalities and thromboembolic events were less frequent (8%, respectively). Our more interesting results were about imaging data, firstly about bed cyst incidence. Retrospective analysis of data showed surgical bed cyst occurrence in 21 of the 36 patients (58%) at the 1-month MRI (Table 3). We analysed the possible relationship between bed cyst and adverse events (Table 3). At 1-month MRI investigation, among patients affected by bed cysts, 57% were asymptomatic and 43% were symptomatic. However, 90% of patients developing one or more adverse events had a concomitant bed cyst. We observed a significant association between intracranial hypertension symptoms and surgical bed cyst (OR 7.35; $p=.019$). We argued that bed cyst occurrence

Table 3 Radiological findings at 1-month MRI

1-Month MRI (<i>n</i> =36)	Cysts (<i>n</i> =21)	No-cyst (<i>n</i> =21)	<i>p</i> Value
Male sex	14 (67%)	10 (67%)	.637
Adverse events	9 (43%)	1 (7%)	.019
Intracranial hypertension	9 (43%)	1 (7%)	.019
Cerebral oedema	5 (24%)	0 (0%)	.053
Healing abnormalities	3 (14%)	0 (0%)	.186
Seizures	2 (9%)	1 (7%)	.627
Revision resection	9 (43%)	9 (60%)	.912
Subtotal resection	13 (62%)	3 (20%)	.014
<i>n</i> wafer implanted, median [IQR]	8 [4–8]	8 [4–8]	.679

was needed even if not sufficient for symptoms presentation. However, we observed that bed cysts were associated to some adverse events above all when patients were preoperatively affected by large tumours located in eloquent areas. Seventeen percent of our patients were not included in the study because of the incomplete radiological follow-up. These patients reported a similar rate of clinical complication (32%). However, we have no MRI data about these patients to assess cyst occurrence.

Cysts showed a benign behaviour: they usually reached the maximal extension at the 1-month MRI and subsequently appeared decreased in volume at 3-month MRI (100% of cases; Figs. 1, 2 and 3). Symptoms followed cyst's course: patients developed raised intracranial pressure-

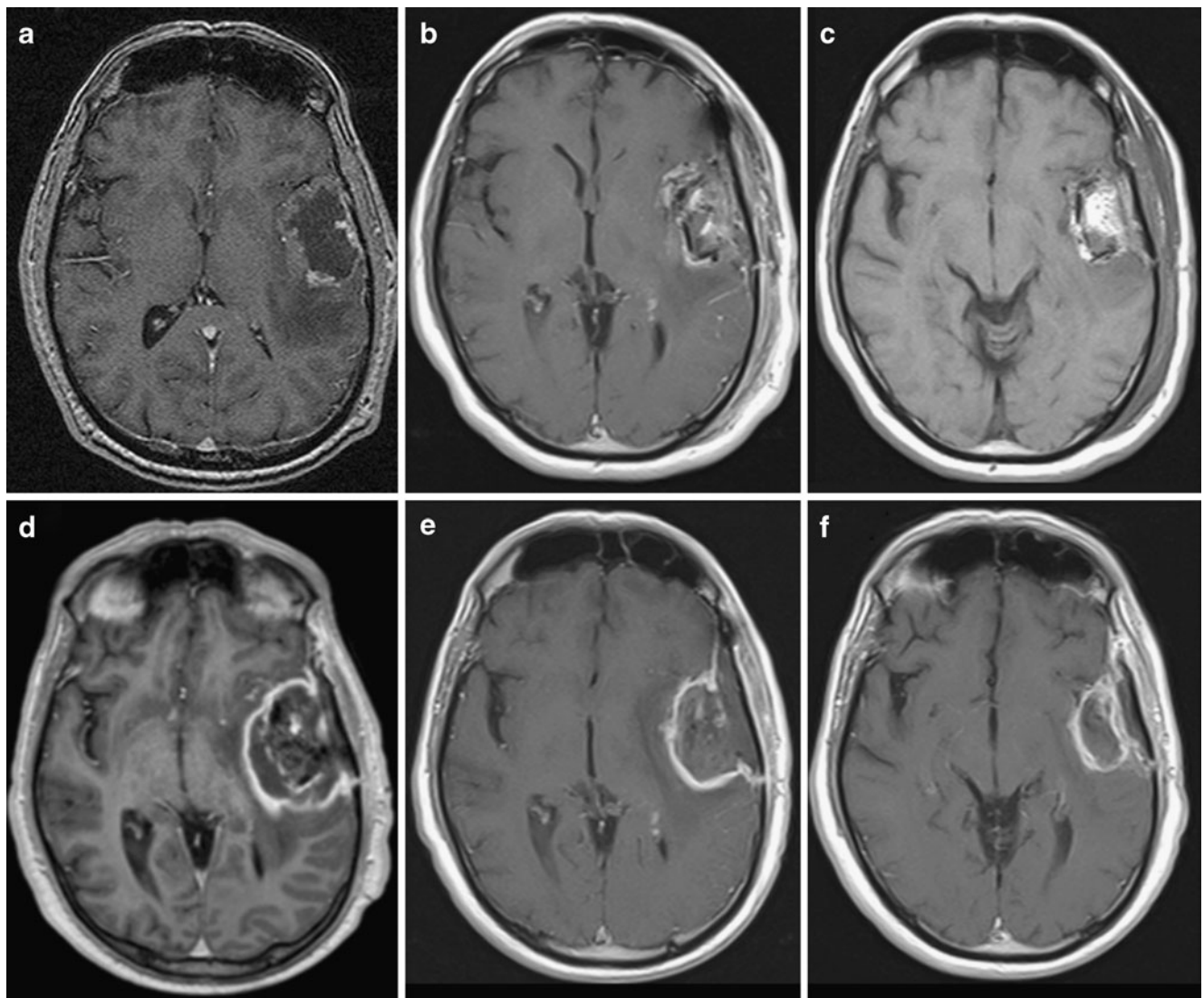


Fig. 1 M/57 Y, newly diagnosed right temporal GBM. MRI T1-weighted axial images after Gadolinium administration: pre-operative stage (a), post-operative (<48 h after surgery) (b), 7 days (c), 1 month (d), 3 months (e), 5 months (f) after surgery; 1-month

MRI shows an enlarged surgical bed with enhancing margins and “spherical” shape (d). The cyst appears decreased in volume gradually at the 3- and 5-month MRI (e, f)

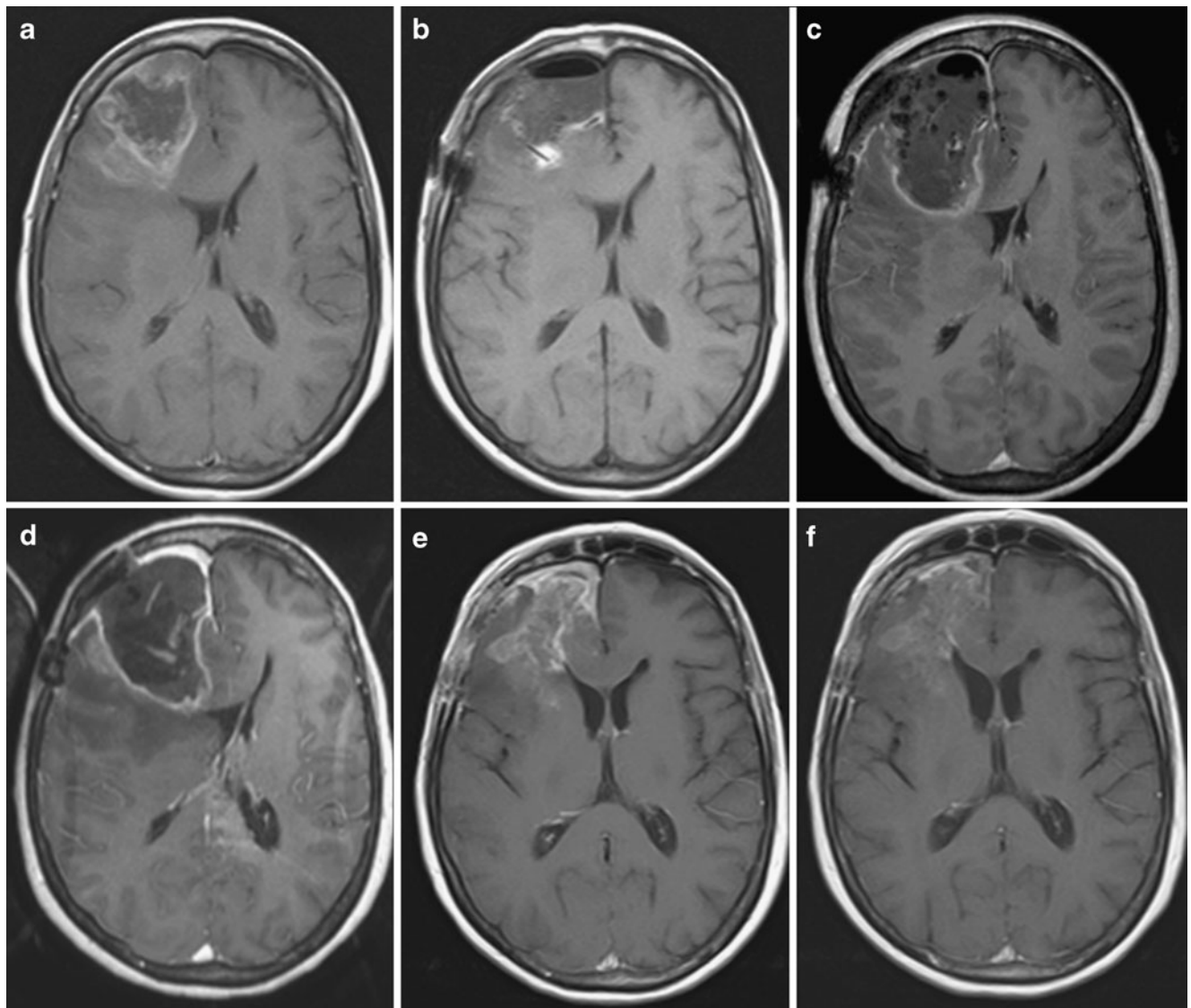


Fig. 2 F/65 Y, newly diagnosed right frontal GBM. MRI T1-weighted axial images after Gadolinium administration: pre-operative stage (a), post-operative stage (<48 hr after surgery) (b), 7 days (c), 1 month (d), 3 months (e), 5 months (f) after surgery; 7-day MRI already shows an enlarged surgical bed with enhancing margins, “spherical” shape, and almost no oedema surrounding the cyst (c). At

the 1-month MRI, the lesion appears grown, surrounded by important oedema and shifting the midline (d). Patient deteriorated so her hospitalisation was decided. After high-dose e.v. corticosteroid treatment the symptoms regressed completely, and the cyst appears decreased in volume at the 3- and 5-month MRI (e, f)

related symptoms approximately 1 month after surgery and improved during following months. In addition, we analysed the possible relationship between cyst occurrence and some clinical and surgical data in order to identify some risk factors for cyst development. We observed only a higher rate of bed cyst when tumour removal was subtotal, with an OR of 5.67 ($p=0.014$). Conversely, it was found no correlation between cysts and number of wafers implanted, patients’ age, WHO grade, tumour recurrence or radio-treatment. Finally, 83% of the patients with bed cyst detection at the 1-month MRI were presenting initial cyst’s growing signs at the 7-day MRI (Fig. 2).

Comparison our relevant results to results from other relevant studies

We recorded safety data similar to what previously reported in larger studies [2, 14]. Safety and efficacy of BCNU wafers treatment after surgical removal of high-grade gliomas are well described by two phase III [3, 25] and 23 non-phase III studies [19]. According to published data [3, 9, 19, 25], intracranial hypertension and healing abnormalities were the adverse events mainly reported after BCNU wafers implantation. Variations in data collection, study design, centre’s experience, corticosteroids’ use,

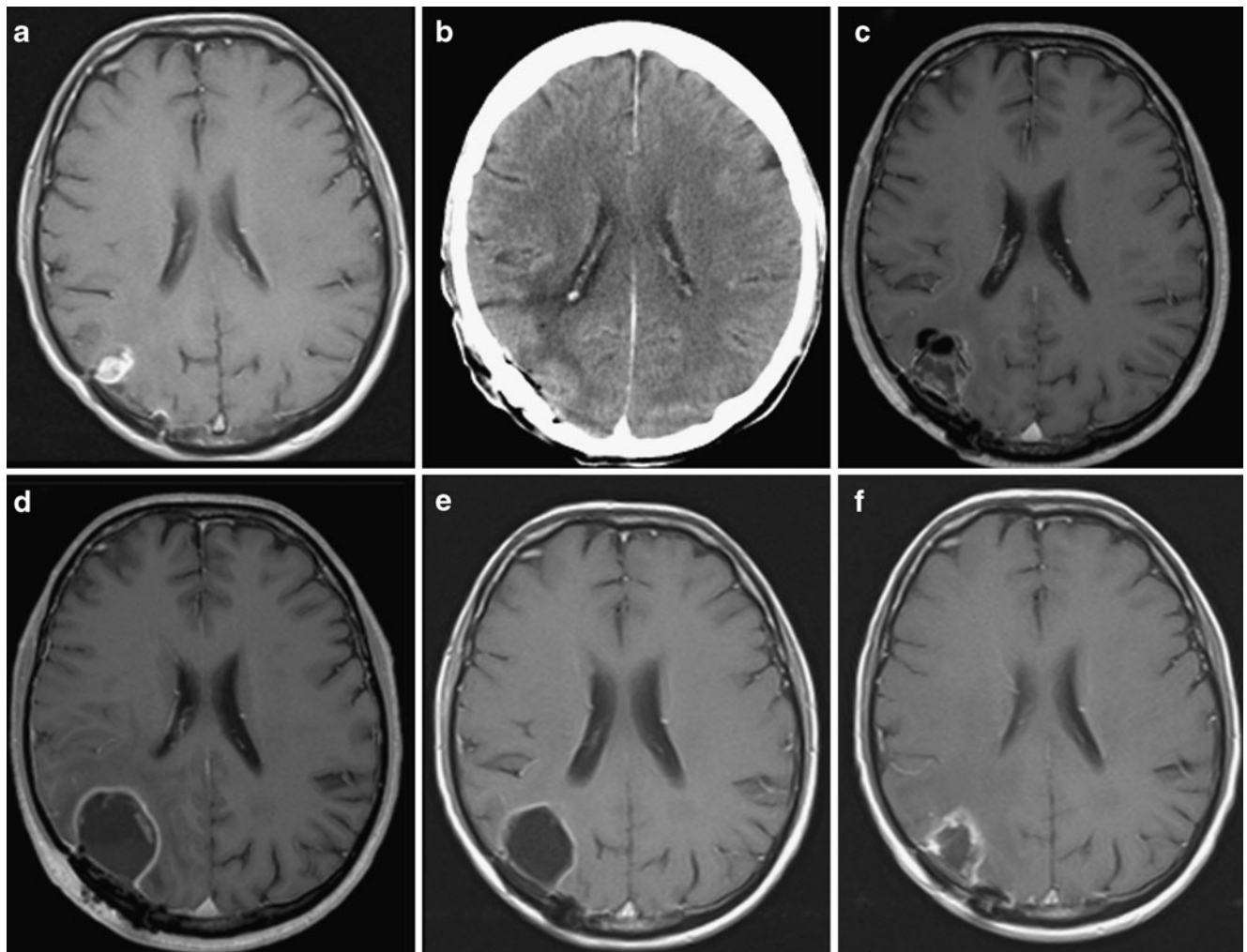


Fig. 3 M/62 Y, recurrent right parietal lobe GBM. MRI T1-weighted axial images after Gadolinium administration: pre-operative stage (a), post-operative CT (<48 hr after surgery) (b), 7 days (c), 1 month (d), 3 months (e), 5 months (f) after surgery; 7-day MRI shows a surgical bed cyst with enhancing margins and “spherical” shape. BCNU wafers are displaced towards the cavity edges, suggesting the presence of positive pressure (d). The cyst’s volume appears gradually decreased at the 3- and 5-month MRI (e, f)

perimeter of the cavity (c). At the 1-month MRI is evident a surgical bed cyst with enhancing margins and “spherical” shape. BCNU wafers are displaced towards the cavity edges, suggesting the presence of positive pressure (d). The cyst’s volume appears gradually decreased at the 3- and 5-month MRI (e, f)

might partially explain adverse events incidence differences between various authors [19]. Despite the large clinical use of BCNU wafers also large experience reports lack of radiological data concerning the postoperative period of these patients [2]. Actually, although wafers locally release more than 70% of Carmustine over the first weeks, we are deficient in radiological data concerning this time window. To date, bed cyst is an unusual report in the postoperative course of patients operated for malignant glioma. In literature some authors reported a 16% rate of cyst formation among GBM patients, whose 60% were symptomatic. However, we are not allowed to make a comparison with our data because they referred about a later period in the post-operative course that was after radio-therapeutic treatment [23]. Even if the event is considered likelier among patients treated with BCNU wafers implantation, a

recent review comprehensive of published larger clinical series has reported only a 0.1% incidence (range 0–11.1%) [19]. The lower incidence than expected is probably to refer to the scarceness of radiological data within first 3 months after surgery. In fact, both phase III and non-phase III studies’ design did not include a first postoperative period radiological monitoring [3, 19, 25]: according to NCCN guidelines [17], radiological follow-up of patients operated for high-grade glioma was routinely composed by a postoperative MRI (before the following 48 h) and by a 3-month MRI to assess radio-treatment effect. Consequently, no data on 1-month MRI in BCNU wafer-treated patients are available in literature to compare our observations about this particular stage. Concerning the relationship of bed cyst with adverse events and with cyst’s course, only few data have been reported in literature. It is

important to emphasise that all papers were case reports referring exclusively to symptomatic patients and that no more than four total cases were described in each report. Intracranial hypertension-related symptoms were principal clinical findings, being probably related to cyst's mass effect and surrounding oedema [7, 8, 12–14]. Most of patients presenting with this new local mass with contrast-enhancing margins introduced a diagnostic problem so revision surgery was not infrequently performed in the clinical suspicion of tumour recurrence [7, 8, 12–14]. No data are available in literature on the better management of bed cysts since the few reported cases were equally treated by surgery and corticosteroid therapy [7, 8, 13, 14, 23]. Finally, literature completely lack of data about supposed predisposing factors and early signs or time of cyst arising.

Strengths and weaknesses of the present study

Strength of the study is the homogeneity of population (high-grade gliomas patients), of surgical treatment (mono-institutional study), of post-operative treatment (radiotherapy and chemotherapy as above reported) and of post-operative investigations (MRI sequences, timing of investigations).

Weakness of the study is due to the lack of a retrospective, non-randomised but stratified, non-wafer control cohort.

Significance of our relevant results and indications for further research

The design of our study does not enable us to change current management of BCNU wafer-treated patients. However, our data provide helpful information about a crucial period of these patients that up to now has not been radiologically investigated. Bed cyst incidence and usual time of occurrence are important issues because bed cyst can represent a diagnostic pitfall. Besides, knowledge of the frequent occurrence of surgical bed cyst over the first 3 months after BCNU wafers implant can be helpful to achieve correct diagnosis when a ring-enhancing mass is detected in a symptomatic patient. In fact, bed cyst has to be differentiated both by surgical cave infection and by tumour recurrence. This is even more important if we consider divergent treatment strategy required by the events. Familiarity with the cyst occurrence in BCNU wafer-treated patients is important to correctly monitor and untimely treat a possible evolving phenomenon. It is interesting to note that patients who presented one or more adverse event were frequently affected by bed cyst. We could argue that BCNU wafer patients affected by a bed cyst should be more carefully monitored for an adverse event. In our experience, 7-day MRI was recurrently able to early detect arising cyst. However, only differently designed studies

could investigate if a specific follow-up could influence clinical outcome of patients. Cyst detection influenced our clinical management of patients. In fact, clinical monitoring was more rigorous and corticosteroid treatment more aggressive when early cyst's signs were detected. Patients underwent high-dose corticosteroid treatment as long as gradual decrease of symptomatic cyst's size was observed. Conversely, asymptomatic patients affected by bed cyst were carefully monitored, but corticosteroid therapy was tapered after 1-month MRI. The result was that no clinical sequelae were recorded and no revision surgeries were needed. We could finally argue that bed cyst in the surgical cavity of BCNU wafer-treated patient is a frequent but benign phenomenon and that corticosteroid therapy is usually sufficient to manage these patients. Again, only further studies could define if such clinical approach could ameliorate safety data.

Conclusions

In our series of patients treated with BCNU wafers, we recorded a higher surgical bed cyst occurrence than what expected. Patients who developed intracranial hypertension or cerebral oedema were most frequently (90%) affected by bed cysts ($p=0.019$). No data on 1-month MRI in BCNU wafer-treated patients are reported in literature to compare our observations. The diagnosis of the event could be important to the better management of these patients. Undoubtedly, we have to underline the limits of our report as it was a non-prospective study in a small series of patients. However, we believe that further investigations in the management of postoperative course could be important in the improvement of the outcome in implanted patients.

Acknowledgments This work was supported in part by Grant Ricerca Sanitaria Finalizzata 285/08 of Regione Veneto.

Conflict of Interest None

References

1. Asher AL (2007) Prospective analysis of temozolomide as adjuvant to Gliadel and radiation in newly diagnosed malignant glioma. Abstract presented at the Annual Meeting of the American Association of Neurological Surgeons, Washington, DC, 2007
2. Attenello FJ, Mukherjee D, Datto G, McGirt MJ, Bohan E, Weingart JD, Olivi A, Quinones-Hinojosa A, Brem H (2008) Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 15:2887–2893
3. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Clifford Schold S (1995) 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* 345:1008–1012
4. Dal Pan G, Butler L, Schactman M (1997) Preliminary analysis of the GLIADEL treatment protocol. Abstract presented at the ASCO Annual Meeting, Atlanta, GA, 1997
 5. Darachiev BJ, Albright RE, Breneman JC, Warnick RE (2008) Safety and efficacy of permanent iodine-125 seed implants and carmustine wafers in patients with recurrent glioblastoma multiforme. *J Neurosurg* 108:236–242
 6. Eisai Inc. Gliadel Wafer: Heath Care Professionals. Available at: http://www.gliadel.com/docs/pdf/Gliadel_PI.pdf [Last accessed 2 February 2010]
 7. Engelhard HH (2000) Tumor bed cyst formation after BCNU wafer implantation: report of two cases. *Surg Neurol* 53:220–224
 8. Engelhard HH, Maher de Leon ME, Rozental JM (1998) Tumor bed cyst formation after BCNU wafer implantation. Abstract presented at the Annual Meeting of the Congress of Neurological Surgeons, Seattle, WA, 1998
 9. Giese A, Bock HC, Kantelhardt SR, Rohde V (2010) Risk management in the treatment of malignant gliomas with BCNU wafer implants. *Cent Eur Neurosurg Jan* 8 doi:10.1055/s-0029-1242775
 10. Gonza'lez Vidal D (2006) The safety of Gliadel implants during the indication period in recurrent surgery in the treatment of glioblastoma multiforme [abstract]. *Neurocirugia* 17:77–78
 11. Gururangan S, Cokgor L, Rich JN, Edwards S, Affronti ML, Quinn JA, Herndon JE 2nd, Provenzale JM, McLendon RE, Tourt-Uhlig S, Sampson JH, Stafford-Fox V, Zaknoen S, Early M, Friedman AH, Friedman HS (2001) Phase I study of Gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. *Neuro-Oncology* 3:246–250
 12. Kleinberg LR, Weingart J, Burger P, Grossman CK, SA Li K, Olivi A, Wharam MD, Brem H (2004) Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 22:1–9
 13. LaRocca R, Glisson S, Hargis J, Petruska D, Villanueva W, Morassutti D, Horne D, Amin-Zimmerman F (2005) High-grade glioma treated with surgery; carmustine wafer; postoperative radiation; and procarbazine, lomustine, and vincristine chemotherapy. *Neurosurg Q* 15:167–171
 14. McGirt MJ, Villavicencio AT, Bulsara KR, Friedman HS, Friedman AH (2002) Management of tumor bed cysts after chemotherapeutic wafer implantation. report of four cases. *J Neurosurg* 96:941–945
 15. McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, Lattera J, Kleinberg LR, Grossman SA, Brem H, Quiñones-Hinojosa A (2009) Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg* 110(3):583–588
 16. McGovern PC, Lautenbach E, Brennan PJ, Lustig RA, Fishman NO (2003) Risk factors for post-craniotomy surgical site infection after 1, 3-bis(2-chloroethyl)-1-nitrosourea (Gliadel) wafer placement. *Clin Infect Dis* 36:759–765
 17. NCCN (2009) NCCN guidelines. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp [Last accessed 2 February 2010]
 18. Pan E, Mitchell SB, Tsai JS (2008) A retrospective study of the safety of BCNU wafers with concurrent temozolomide and radiotherapy and adjuvant temozolomide for newly diagnosed glioblastoma patients. *J Neuro-oncol* 88:353–357
 19. Sabel M, Giese A (2008) Safety profile of carmustine wafers in malignant glioma: a review of controlled trials and a decade of clinical experience. *Curr Med Res Opin.* 2008 Oct 20. doi:10.1185/03007990802508180
 20. SubachBR, WithamTF, KondziolkaD, LunsfordLD, BozikM, SchiffD (1999) Morbidity and survival after 1, 3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 45:17–22
 21. Tait MJ, Critchley GR (2006) Experience of revision craniotomy for debulking of high grade gliomas in 27 patients in a single UK centre, with and without insertion of carmustine wafers. Meeting of the Society of British Neurosurgeons, Preston, UK, 2006
 22. Uff CEG, Bradford R (2005) Use of Gliadel (BCNU) Wafers in high grade glioma. Abstract presented at the meeting of the Society of British Neurosurgeons, Plymouth, UK, 2005
 23. Volc D, Jellinger K, Flament H, Böck F, Klumair J (1981) Cerebral space-occupying cysts following radiation and chemotherapy of malignant gliomas. *Acta Neurochir (Wien)* 57:177–193
 24. Weingart J, Grossman SA, Carson KA, Fisher JD, Delaney SM, Rosenblum ML, Olivi A, Judy K, Tatter SB, Dolan ME (2007) 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* 25:399–404
 25. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jääskeläinen J, Ram Z (2003) A Phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-Oncology* 5:79–88