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Update

Carmustine wafer implantation for high-grade gliomas: Evidence-based safety efficacy and practical recommendations from the Neuro-oncology Club of the French Society of Neurosurgery

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ABSTRACT

There is a growing body of evidence that carmustine wafer implantation during surgery is an effective therapeutic adjunct to the standard combined radio-chemotherapy regimen using temozolomide in newly diagnosed and recurrent high-grade glioma patient management with a statistically significant survival benefit demonstrated across several randomized clinical trials, as well as prospective and retrospective studies (grade A recommendation). Compelling clinical data also support the safety of carmustine wafer implantation (grade A recommendation) in these patients and suggest that observed adverse events can be avoided in experienced neurosurgeon hands. Furthermore, carmustine wafer implantation does not seem to impact negatively on the quality of life and the completion of adjuvant oncological treatments (grade C recommendation). Moreover, emerging findings support the potential of high-grade gliomas molecular status, especially the O(6)-Methylguanine-DNA Methyltransferase promoter methylation status, in predicting the efficacy of such a surgical strategy, especially at recurrence (grade B recommendation). Finally, carmustine wafer implantation appears to be cost-effective in high-grade glioma patients when performed by an experienced team and when total or subtotal resection can be achieved. Altogether, these data underline the current need for a new randomized clinical trial to assess the impact of a maximal safe resection with carmustine wafer implantation followed by the standard combined chemoradiation protocol stratified by molecular status in high-grade glioma patients.

1. Introduction

High-grade gliomas (HGGs) (World Health Organization [WHO] grade III and IV gliomas) are the most aggressive primary brain tumors. They are more common in men, and their incidence increases with age. The incidence rate of HGGs, within the French population, varies between 3.34 and 6.09 per 100 000 inhabitants per year [1].

Maximal safe resection, whenever possible using intraoperative imaging navigation tools and functional monitoring, is recommended as the first treatment for newly diagnosed and recurrent HGG and has been shown to reduce symptoms, improve survival, and increase the efficacy of adjuvant therapies [1–11]. During surgical resection, biodegradable wafers releasing 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 [12–14]. Carmustine wafer implantation is proposed for newly diagnosed and recurrent HGG when subtotal (>90% of contrast enhancement) or total resection is performed [15–17]. This local chemotherapy treatment offers a theoretical therapeutic bridge

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during the regular off-period treatment that lies after surgery and before the beginning of adjuvant oncological therapy [4]. Although the efficacy of carmustine wafer implantation is well established, its safety remains a matter of debate, with varying results regarding toxicity, maintaining of the quality of life, and feasibility of adjuvant oncological treatments [18].

On the behalf of the Neuro-Oncology Club of the Société française de neurochirurgie, we aimed to perform an evidence-based analysis of carmustine wafer implantation safety and efficacy in newly diagnosed and recurrent HGG to help in providing practical recommendations for this patient population.

1.1. Standard of care for newly diagnosed HGG

Each oncologic decision should be discussed in a multidisciplinary staff meeting. Following surgery, the current standard of care for newly diagnosed grade IV glioma (glioblastomas) patients under 70-years-old with preserved overall condition consists of radiotherapy (60 Gy, 30 fractions over 6 weeks) with concomitant and adjuvant temozolomide, the standard combined chemoradiotherapy, (level of evidence 1, grade A recommendation) [19,20]. Recently, two randomized controlled trials (RCTs) conducted in Europe and US showed that adding bevacizumab to the standard combined chemoradiotherapy protocol in newly diagnosed WHO grade IV glioma patients, was not associated with an improvement of overall survival (OS) [21,22].

Following surgery, the current standard of care for newly diagnosed grade III gliomas (anaplastic gliomas) for patients under 70-year-old depends on glioma molecular subtype. For isocitrate dehydrogenase (IDH)-mutated 1p19q codeleted WHO grade III oligodendrogliomas, the current standard of care consists of sequential radiotherapy and chemotherapy using procarbazine, lomustine and vincristine (PCV) [23,24] (level of evidence 1, grade A recommendation). For IDH-mutated WHO grade III astrocytomas without 1p19q codeletion, there is currently no standard of care. Standard combined chemoradiotherapy, radiotherapy followed by adjuvant chemotherapy using temozolomide or PCV can be proposed [25] (level of evidence 3, grade C recommendation). For IDH-wild-type WHO grade III astrocytomas without 1p19q codeletion, there is also no standard of care. Standard combined chemoradiotherapy or radiotherapy followed by adjuvant chemotherapy with Temozolomide could be proposed [25] (level of evidence 3, grade C recommendation).

For patients over 70-years-old, the current standard of care for newly diagnosed grade IV glioma (glioblastomas) with preserved overall condition consists of short-course radiotherapy (40 Gy, 15 fractions over 3 weeks) with concomitant and adjuvant temozolomide (level of evidence 1, grade A recommendation) [26]. For other high-grade glioma subtypes, there is no standard of care and oncological treatment depends on a multidisciplinary discussion, which takes into account the global condition of the patient [27–31].

1.2. Standard of care for recurrent HGG

For recurrent grade III or IV gliomas, whatever the patient's age and overall condition, there is currently no standard of care. The choice of the oncological treatment depends on a multidisciplinary discussion, which takes into account the previous therapeutic modalities, and the global condition of the patient. Surgical resection, radiotherapy, chemotherapy or supportive care could be proposed (level of evidence 2–3, grade B–C recommendation) [32–41].

2. Carmustine wafer technology

Carmustine wafer (Gliadel®, Kyowa Hakko Kirin Co) is a biodegradable copolymer disc releasing the alkylating agent Carmustine (1,3-bis(2-chloreoethyl)-1-nitrosourea, BCNU). Each implant contains 7.7 mg of Carmustine and 192.3 mg of polifeprosan 20 (inactive ingredient), which induce cell-cycle arrest and apoptosis by alkylating DNA and inhibiting nucleic acid synthesis [42]. Carmustine wafers delivers chemotherapy directly into the surgical cavity. Pharmacological studies in rabbit models showed that the delivery of carmustine inside the brain tissue is extended at high concentrations up to 12 mm from the wafer site [43]. Beyond this, the brain tissue is exposed to lower concentrations of carmustine [42]. The carmustine release time is 21 days but the majority is released between 5 and 7 days [43,44] and complete degradation of the wafers occurs between the 6th and 8th weeks [43,45,46].

3. Search methodology

A literature search was conducted on PubMed to identify phase I and II studies, randomized clinical trials (RCTs), prospective cohort studies, and retrospective studies concerning carmustine wafer implantation (case reports excluded) in English language. The inclusive search dates were from January 1992 through October 2016. Specific search terms included Gliadel® and carmustine wafer. Relevant studies were classified according to the level of evidence (1, 2, 3-4) and to the grade of recommendation (A, B or C) in accordance with the French National Authority for Health - Haute Autorité de santé (HAS) (Table 1). We used the RIGHT reporting tool for practice guidelines in health care to strengthen the methodology [47].

4. Evidence-based data of carmustine wafers efficacy for newly diagnosed HGG

4.1. Highest level of evidence (level 1) with grade A recommendation

Two multicenter RCTs [13,14] and one long-term follow-up analysis of the largest RCT [41] assessed the efficacy of carmustine wafer implantation in newly diagnosed HGG. In both studies, patients were randomized to carmustine or placebo wafers implantation followed by adjuvant radiotherapy, which was the standard of care at that time for grade III and grade IV gliomas. These two RCTs showed that carmustine wafer implantation significantly improved OS.

The first RCT assessing carmustine wafer implantation in newly diagnosed HGG was performed in 1997 by Valtonen et al., who conducted a multicenter Finnish RCT, which included 32 patients with newly diagnosed HGG – 16 in each group – (27 grade IV gliomas, 5 grade III gliomas) [13]. The small number of included patients, due to the fact that Carmustine wafers were no longer available,

Table 1
Grades of recommendation and levels of evidence according to the French National Authority for Health (Haute Autorité de santé).

Grade of recommendation	Level of evidence	Study types
A - scientific evidence	1	Well-conducted randomized controlled trials Meta-analysis including randomized controlled trials Decision analysis based on well-conducted studies
B - scientific presumption	2	Randomized controlled trials with biases Well-conducted non-randomized comparative studies Cohort studies
C - low level of scientific evidence	3–4	Case-control studies Comparative studies with significant biases Retrospective studies Descriptive epidemiological studies