Carmustine wafer

Carmustine (BCNU) implants (Gliadel® Wafer, Eisai Inc., New Jersey, USA) for the treatment of malignant gliomas (MGs) were shown to enhance overall survival in comparison to placebo in controlled clinical trials in the United States and Europe.

A prospective, multicenter phase I/II study involving Japanese patients with MGs was performed to evaluate the efficacy, safety, and pharmacokinetics of BCNU implants. The study enrolled 16 patients with newly diagnosed MGs and 8 patients with recurrent MGs. After the insertion of BCNU implants (8 sheets maximum, 61.6 mg BCNU) into the removal cavity, various chemotherapies (including temozolomide) and radiotherapies were applied. After placement, overall and progression-free survival rates and whole blood BCNU levels were evaluated. In patients with newly diagnosed MGs, the overall survival rates at 12 months and 24 months were 100.0% and 68.8%, and the progression-free survival rate at 12 months was 62.5%. In patients with recurrent MGs, the progression-free survival rate at 6 months was 37.5%. There were no grade 4 or higher adverse events noted due to BCNU implants, and grade 3 events were observed in 5 of 24 patients (20.8%). Whole blood BCNU levels reached a peak of 19.4 ng/mL approximately 3 hours after insertion, which was lower than 1/600 of the peak BCNU level recorded after intravenous injections. These levels decreased to less than the detection limit (2.00 ng/mL) after 24 hours. The results of this study involving Japanese patients are comparable to those of previous studies in the United States and Europe [1)].

Complications

see Carmustine wafer complications.

Systematic reviews

The following databases were searched: CENTRAL (issue 4. 2010); MEDLINE and EMBASE. The original search strategy also included: Science Citation Index; Physician Data Query; and the meta-Register of Controlled Trials. Reference lists of all identified studies were searched. The Journal of Neuro-Oncology and Neuro-oncology were hand searched from 1999 to 2010, including all conference abstracts. Neuro-oncologists, trial authors and drug manufacturers were contacted regarding ongoing and unpublished trials. SELECTION CRITERIA:

Patients included those of all ages with a histologically proven diagnosis of HGG (using intra-operative analysis when undergoing first resection). Therapy could be instigated for either newly diagnosed disease (primary therapy) or at recurrence. Interventions included insertion of chemotherapy wafers to the resection cavity. Included studies had to be randomised controlled trials (RCTs). DATA COLLECTION AND ANALYSIS:

Two independent review authors assessed the search results for relevance and undertook critical appraisal according to pre-specified guidelines. MAIN RESULTS:

In primary disease two RCTs assessing the effect of carmustine impregnated wafers (Gliadel®) and enrolling a total of 272 participants were identified. Survival was increased with Gliadel® compared to placebo (hazard ratio (HR) 0.65, 95% Confidence Interval (CI) 0.48 to 0.86, P = 0.003). In recurrent

disease a single RCT was included comparing Gliadel® with placebo and enrolled 222 participants. It did not demonstrate a significant survival increase (HR 0.83, 95% CI 0.62 to 1.10, P = 0.2). There was no suitable data for any of the secondary outcome measures. Adverse events were not more common in either arm and are presented in a descriptive fashion. AUTHORS' CONCLUSIONS:

Carmustine impregnated wafers (Gliadel®) result in improved survival without an increased incidence of adverse events over placebo wafers when used for primary disease therapy. There is no evidence of benefit for any other outcome measures. In recurrent disease Gliadel® does not appear to confer any additional benefit [2)].

Case series

One of the therapeutic options for Glioblastoma multiforme includes placing biodegradable wafers releasing BCNU (Gliadel®) into the tumor bed at the time of surgical removal of the tumor. Due to the significant benefit this polymer technology has had clinically, Shapira-Furman et al., from Johns Hopkins Hospital have prepared wafers releasing Temozolomide (TMZ), TMZ delivered via polymer wafer could be used as a complementary treatment with or as an alternative to Gliadel®. TMZ is an alkylating agent which is water soluble. To remain comparable with the preclinical studies that led to Gliadel® the same size of wafers were formulated with TMZ. Wafers were loaded with 50% w/w TMZ in poly(lactic acid-glycolic acid) (PLGA) and showed reliable release of high dose TMZ for a period of 4 weeks. To achieve this 30-day release of the highly water soluble drug, they developed an encapsulation method, where the drug powder was first coated with the polymer to form core-shell particles in which the coating shell served as a rate controlling membrane for the drug particles. Wafers were also made with a co-loading of TMZ and BCNU. All wafers were tested in vivo by treating an intracranial 9L gliosarcoma model in F344 rats. Rats that were either untreated or treated with blank wafer died within 11 days while the median survival for rats treated with systemic TMZ was 18 days. The group that received the BCNU alone wafer had a median survival of 15 days, the group that received the TMZ wafer alone had a median survival of 19 days, and the group treated with the BCNU-TMZ wafer had a median survival of 28 days with 25% of the animals living long term ($p < .0038$ vs. Control; $p < .001$ vs. Blank Polymer). These findings demonstrate the potential of this newly designed wafer for treating GBM. Moreover, this concept, can pave the way for other drug combinations that may improve the clinical application of numerous agents to treat solid tumors [3)].

2017

Patients with recurrent glioblastoma operated on between 2007 and 2014 were divided into 3 groups: >65 years with carmustine wafer (BCNU wafer) implantation, >65 years without BCNU wafer implantation, and ≤65 years with BCNU wafer implantation. We compared survival and complications.

A total of 79 patients were identified: 24 in the older BCNU group (median age 68.2 years, 33.3% with a methylated MGMT promoter), 16 in the older non-BCNU group (median age 68.6 years, 31.3% with a methylated O6 methylguanine DNA methyltransferase), and 39 in the younger BCNU group (median age 56.8 years). Survival after progression was 9.2 months in the elderly BCNU group and 7.6 months in the elderly non-BCNU group ($p = 0.34$); overall survival was 17.2 and 15.9 months, respectively ($p = 0.35$). Klein et al. found a tendency toward a higher rate of seizures and pneumonia in the older BCNU group.

BCNU wafer implantation after resection of recurrent GBM is a reasonably safe treatment in patients aged >65 years. Seizures and systemic infections may occur more frequently, but the trade-off is still

favorable as survival may be influenced positively. Higher age should not be regarded as a contraindication for BCNU wafers [4].

2015

Carmustine wafer implantation during surgical resection followed by the standard chemoradiation protocol for newly diagnosed glioblastoma in adults resulted in a significant progression-free survival benefit [5].

2013

A retrospective study of 47 patients with either newly diagnosed (30 patients) or recurrent glioblastoma (17 patients) treated with BCNU (bis-chloroethylnitrosourea) wafers. Thirteen of the newly diagnosed patients received local BCNU and irradiation only (first-line BCNU), while 17 patients additionally received concomitant and adjuvant temozolomide (TMZ) radiochemotherapy (first-line BCNU + TMZ). Of the 17 patients treated for recurrent glioblastoma (second-line BCNU), 16 had received radiotherapy with concomitant and adjuvant TMZ as an initial treatment. Median overall survival (OS) did not significantly differ between 19 patients with MGMT promoter methylated tumors when compared to 28 patients with unmethylated tumors (18.9 vs 15.0 months; p = 0.1054). In the first-line BCNU + TMZ group, MGMT promoter methylation was associated with longer OS (21.0 vs 11.1 months, p = 0.0127), while no significant survival differences were detected in the other two subgroups. Progression-free survival did not significantly differ between patients with and without MGMT promoter methylated tumors in the entire patient cohort or any of the three subgroups. The first-line BCNU + TMZ group showed no significant difference in OS when compared to the first-line BCNU group (18.9 vs 14.7 months), but tended to have more therapy-related adverse effects (53% vs 24%, p = 0.105). In summary, MGMT promoter methylation showed a non-significant trend toward longer survival in our patient cohort. The combination of TMZ radiochemotherapy with local delivery of BCNU did not provide a significant survival benefit compared to local BCNU alone, but was associated with a higher rate of adverse effects. Owing to the small number of patients investigated, however, these findings would need to be corroborated in larger patient cohorts [6].

2000

Patients were treated with a second craniotomy for tumor resection and placement of carmustine wafers. After implantation, the first patient did well for 6 weeks, then developed lethargy, headaches, and vomiting. CT scan showed a large cyst at the craniotomy site; this required reoperation for drainage. The second patient had a seizure, deterioration of mental status, and progressive hemiparesis 10 days after wafer implantation. CT scan again showed that a large cyst had formed in the area of the previous surgery; she also required reoperation. In each case, minimal tumor and no evidence of infection were found. Within a few more weeks, each patient succumbed to progressive disease.

The hypodense, roughly spherical cysts clearly demonstrated clinically significant mass effect, and required reoperation despite treatment with high-dose corticosteroids. Neurosurgeons should be alert to the possibility of tumor bed cyst formation in patients treated with interstitial BCNU wafers [7].

1)

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