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First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience.

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Abstract

Randomized phase III trials have shown significant improvement of survival 1, 2, and 3 years after implantation of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) wafers for patients with newly diagnosed malignant glioma. But these studies and subsequent non-phase III studies have also shown risks associated with local chemotherapy within the central nervous system. The introduction of concomitant radiochemotherapy with temozolomide (TMZ) has later demonstrated a survival benefit in a phase III trial and has become the current treatment standard for newly diagnosed malignant glioma patients. Lately, this has resulted in clinical protocols combining local chemotherapy with BCNU wafers and concomitant radiochemotherapy with TMZ although this may carry the risk of increased toxicity. We have compiled the treatment experience of seven neurosurgical centers using implantation of carmustine wafers at primary surgery followed by 6 weeks of radiation therapy (59-60 Gy) and 75 mg/m²/day TMZ in patients with newly diagnosed glioblastoma followed by TMZ monochemotherapy. We have retrospectively analyzed the postoperative clinical course, occurrence and severity of adverse events, progression-free interval, and overall survival in 44 patients with newly diagnosed glioblastoma multiforme. All patients received multimodal treatment including tumor resection, BCNU wafer implantation, and concomitant radiochemotherapy. Of 44 patients (mean age 59 +/- 10.8 years) with glioblastoma who received Gliadel wafer at primary surgery, 28 patients (64%) had died, 16 patients (36%) were alive, and 15 patients showed no evidence of clinical or radiographic progression after a median follow-up of 15.6 months. At time of analysis of adverse events in this patient population, the median overall survival was 12.7 months and median progression-free survival was 7.0 months. Surgical, neurological, and medical adverse events were analyzed. Twenty-three patients (52%) experienced adverse events of any kind including complications that did not require treatment. Nineteen patients (43%) experienced grade 3 or grade 4 adverse events. Surgical complications included cerebral edema, healing abnormalities, cerebral spinal fluid leakage, meningitis, intracranial abscess, and hydrocephalus. Neurological adverse events included newly diagnosed seizures, alteration of mental status, and new neurological deficits. Medical complications were thromboembolic events (thrombosis, pulmonary embolism) and hematotoxicity. Combination of both treatment strategies, local chemotherapy with BCNU wafer and concomitant radiochemotherapy, appears attractive in aggressive multimodal treatment schedules and may utilize the sensitizing effect of TMZ and carmustine on MGMT and AGT on their respective drug resistance genes. Our data demonstrate that combination of local chemotherapy and concomitant radiochemotherapy carries a significant risk of toxicity that currently appears underestimated. Adverse events observed in this study appear similar to complication rates published in the phase III trials for BCNU wafer implantation followed by radiation therapy alone, but further add the toxicity of concomitant radiochemotherapy with systemic TMZ. Save use of a combined approach will require specific prevention strategies for multimodal treatments.

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