

**Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas: phase I clinical results**

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Non-invasive loco-regional electro-hyperthermia (EHT) plus alkylating chemotherapy is occasionally used as salvage treatment in the relapse of patients with high-grade gliomas. Experimental data and retrospective studies suggest potential effects. However, no prospective clinical results are available. We performed a single-center prospective non-controlled single-arm Phase I trial.

Main inclusion criteria were recurrent high-grade glioma WHO Grade III or IV, age 18-70, and Karnofsky performance score  $\geq 70$ . Primary endpoints were dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) with the combined regimen. Groups of 3 or 4 patients were treated 2-5 times a week in a dose-escalation scheme with EHT. Alkylating chemotherapy (ACNU, nimustin) was administered at a dose of 90 mg/m<sup>2</sup> on day 1 of 42 days for up to six cycles or until tumor progression (PD) or DLT occurred. Fifteen patients with high-grade gliomas were included. Relevant toxicities were local pain and increased focal neurological signs or intracranial pressure. No DLT occurred. In some patients, the administration of mannitol during EHT or long-term use of corticosteroids was necessary to resolve symptoms. Although some patients showed responses in their primarily treated sites, the pattern of response was not well defined. EHT plus alkylating chemotherapy is tolerable in patients with relapse of high-grade gliomas. Episodes of intracranial pressure were, at least, possibly attributed to EHT but did not cause DLTs. A Phase II trial targeting treatment effects is warranted on the basis of the results raised in this trial.