Enhanced antitumor effect of combined modality treatment using convection-enhanced delivery of hydrophilic nitrosourea with irradiation or systemic administration of temozolomide in intracranial brain tumor xenografts

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Abstract:

Objective: Convection-enhanced delivery (CED) is a local infusion technique that delivers chemotherapeutic agents directly to the central nervous system, circumventing the blood–brain barrier and reducing systemic side effects. We previously reported the safety and efficacy of CED of ACNU (nimustine hydrochloride: 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride), a hydrophilic nitrosourea, in rat brain tumor models. This study evaluated the efficacy of combined-modality treatments using CED of ACNU with irradiation or systemic administration of temozolomide. Methods: Antitumor efficacy and toxicity of the treatment were evaluated using rat 9L intracranial brain tumor models. Results: Combined treatment using CED of ACNU with irradiation produced significantly longer survival time than each treatment alone (versus CED: p<0.001, versus irradiation: p<0.05, logrank test) or systemic administration of ACNU with irradiation (p<0.001). Long-term survival (120 days) and eradication of tumor occurred only in this combined-treatment group. We also showed that CED of ACNU plus systemic administration of temozolomide significantly enhanced survival rate compared with each treatment alone (versus CED: p<0.001, versus systemic temozolomide: p<0.05). Discussion: Multimodality treatment using CED of ACNU, radiotherapy and systemic chemotherapy with temozolomide is a promising strategy for treatment of brain tumors.

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