A comprehensive outlook on intracerebral therapy of malignant gliomas.


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Abstract

Glioblastoma multiforme (GBM) is the most frequent and aggressive malignant glioma (MG), with a median survival time of 12-15 months, despite current best treatment based on surgery, radiotherapy and systemic chemotherapy. Many potentially active therapeutic agents are not effective by systemic administration, because they are unable to cross the blood-brain barrier (BBB). As intracerebral administration bypasses the BBB, it increases the number of drugs that can be successfully delivered to the brain, with the possibility of minor systemic toxicity and better effectiveness. This review summarizes the results of the extensive clinical research conducted on intracerebral therapy. Biodegradable drug carriers, implantable subcutaneous reservoirs and convection-enhanced delivery (CED) represent the main techniques for intracerebral delivery, while conventional chemotherapy agents, radiolabeled antibodies and receptor-targeted toxins are the main classes of drugs for intracerebral therapy. At the present time, biodegradable carmustine wafers, commercialized as Gliadel®, are the only FDA-approved treatment for intracerebral chemotherapy of MG, but intracavitary delivery of mitoxantrone and radiolabeled antitenascin antibodies via implantable reservoirs has yielded promising results in uncontrolled trials. The pressure-driven flow generated by CED can potentially distribute convected drugs over large volumes of the brain, independently on their intrinsic diffusivity. Nevertheless, prominent technical problems, like backflow, are yet to be properly addressed and contributed to the disappointing results of two phase III trials that investigated CED of cintredekin besudotox and TransMid™ in patients with recurrent GBM.

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