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The long and winding road—gene therapy for glioma

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Abstract

Gene therapy approaches for glioblastoma multiforme (GBM) have been under investigation in clinical trials since the 1990s, but the results to date have been disappointing. A recently published phase III trial of adenovirus-based gene therapy for GBM has demonstrated modest—but possibly clinically relevant—improvements in patient survival.

Adult glioblastoma multiforme (GBM) is one of the deadliest, most rapidly progressing cancers. Overall median survival for this tumour currently ranges from 16.2 –21.2 months.[1] Younger age and better general health at diagnosis, surgical resection greater than 97%, and increased sensitivity to temozolomide (that is, reduced O^6-methylguanine-DNA methyltransferase [MGMT] activity in tumour cells) are the only reliable positive prognostic factors. Surgical resection is limited by the location of the tumour near eloquent brain areas, and MGMT inhibitors are not yet available. Nevertheless, surgical resection, radiotherapy and temozolomide have all been shown to extend patient survival, and have become the standard of care for GBM.[1]

In an attempt to improve the prognosis for patients with GBM, scientists are exploring additional therapies to be combined with the standard treatment. Since 1996, gene therapy employing vectors expressing the conditionally cytotoxic *HSV1-tk* (herpes simplex virus type 1 thymidine kinase) gene encoded within nonreplicating retroviral vectors has been tested in several clinical trials. Administration of nonreplicating retroviral vectors expressing *HSV1-tk* to the brain was combined with systemic ganciclovir treatment to initiate *HSV1-tk* cytotoxicity. Prompted by occasional positive responses in individual patients, this approach was tested on a population of 248 patients in a phase III clinical trial;[2] no improved survival was reported and the clinical work was halted. As recently reported in *The Lancet Oncology*, however, the gene therapy approach has now been revisited by the ASPECT Study Group.[3]

The latest study by Westphal *et al.* used a nonreplicating adenoviral vector expressing *HSV1-tk* (AdvHSV-tk, also known as sitimagene ceradenovac).[3] In a previous phase I clinical trial,[4] GBM patients treated with AdvHSV-tk had 80% increased survival (450 days) compared with those treated with either retroviral gene therapy (222 days) or controls (249 days). In an expanded phase II follow-up study, the same group compared 17 patients treated with AdvHSV-tk with 19 patients randomly assigned to receive control vectors. AdvHSV-tk plus ganciclovir increased survival from 273 days to 494 days (80% improvement).[5] This work provided the impetus for the latest phase III trial.[3]

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Competing interests
The authors declare no competing interests.

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The large multicentre phase III ASPECT trial commenced in 2005 and treated a total of 251 patients randomly allocated to sitimagene ceradenovec and ganciclovir gene therapy plus standard care, or to standard care alone.[3] Patients were recruited at 38 sites in nine different European countries. 119 experimental and 117 control patients could be evaluated at the end of the trial. The trial analysed a composite primary end point (time to death or reintervention) and overall survival. In patients allocated to gene therapy, the time to the primary end point increased by 40 days (308 days versus 268 days) compared with control values, and the median overall survival increased by 45 days (497 days versus 452 days).

Differences in radiotherapy, chemotherapy and surgery were unavoidable, as treatment could not be homogenized across the 38 centres.[3] In addition, temozolomide was introduced as a GBM treatment while this trial was proceeding. As the use of this drug depended on approval and availability in each of the 38 centres, its administration was not universal. Patients were, therefore, treated by a large number of surgeons, and were administered different radiotherapy regimes and offered different chemotherapy options. In view of the lack of treatment standardization, our interpretation is that gene therapy was the main variable over a complex background of various surgical, radiotherapeutic and medical treatments. This complex patient–treatment scenario makes this trial closer to a trial testing new treatments in the general population than to the more tightly controlled experimental settings of phase III trials.

How clinically significant are these findings? The authors report statistical significance for the primary end point, but not for overall survival (note, however, that absolute survival is comparable—40 days versus 45 days—for the primary and overall survival end points). These values were not considered convincing by the European Medicines Agency,[6] and this therapy is thus not currently available for the treatment of patients with GBM.

Given the published history, we can assume that the regulatory agencies and the trial investigators disagreed on the interpretation of the results. Two main challenges must be addressed when interpreting the results of such trials. First, one must demonstrate that criteria exist to determine whether a clinical trial of any phase and patient cohort size has failed and should not be pursued further. This scenario must be distinguished from noisy results that may obscure the existence of a responding subgroup of patients, or a small therapeutic effect. We can determine beyond reasonable doubt when a trial has failed—the retroviral trial,[2] for example, provided sufficient grounds to rule out further pursuit of nonreplicating retroviral therapy. However, we should not disregard clinically relevant effects detected in small trials.[4,5]

Equally challenging is the interpretation of small differences seen in some large clinical trials. If the small differences represent real therapeutic benefits, we should certainly continue to either use or improve such therapies, as cumulative responses to combined treatments have been shown to provide the best survival rates in various cancers. Similarly, a patient who has survived a heart attack has an increased death risk, but treatment with several agents to simultaneously inhibit blot clot formation, block atrial fibrillation, block the renin–angiotensin axis and reduce hypertension, and improve blood lipid patterns (statins), reduces the risk to pre-heart attack values.[7] As this example illustrates, small but effective and cumulative therapeutic effects can provide a treatment that is essentially 100% effective.

Westphal and colleagues[3-5] are to be commended for having followed Richard Dedekind's dictum and tested their potential therapy in the most stringent manner possible. Whether the treatment is effective but its effect size is small, or whether the treatment is ineffective, remains to be decided. In our opinion, the evidence suggests that AdvHSV-tk has a small but

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clinically significant effect, and might be refined by further improvements in trial design, in combination with other approaches. Advantagene, Inc. (Auburndale, MA, USA) is preparing a phase III trial in the USA using AdvHSV-Tk (E. Aguilar-Cordova, personal communication), indicating continued confidence in this approach. Equally, alternative gene therapy approaches for GBM, including replicating adenovirus, replicating retrovirus with conditional cytotoxicity, and replicating poliovirus, are producing suggestive results;[8] their ultimate effectiveness will have to await large phase III randomized controlled trials. In addition, on the basis of promising preclinical evidence, we are about to launch a phase I clinical trial that will combine AdvHSV1-tk with an immunostimulatory cytokine expressed by an adenoviral vector, Ad-Flt3L (IND 14,575).[9]

In science (and medicine), what can be proven should not be believed without proof. Until we have proof of efficacy, we need time, resources to test the new therapies in stringent clinical trials, and infinite stamina and determination. We trust that conclusive clinical trial results will lead to prompt FDA approval to treat patients with GBM.

References

1. Grossman SA, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. Clin Cancer Res. 2010; 16:2443–2449. [PubMed: 20371685]
2. Rainov NG. A phase III clinical evaluation of herpes simplex virus type 1 thymidine kinase and ganciclovir gene therapy as an adjuvant to surgical resection and radiation in adults with previously untreated glioblastoma multiforme. Hum Gene Ther. 2000; 11:2389–2401. [PubMed: 11096443]
3. Westphal M, et al. Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013; 14:823–833. [PubMed: 23850491]
4. Sandmair AM, et al. Thymidine kinase gene therapy for human malignant glioma, using replication-deficient retroviruses or adenoviruses. Hum Gene Ther. 2000; 11:2197–2205. [PubMed: 11084677]
5. Immonen A, et al. AdvHSV-tk gene therapy with intravenous ganciclovir improves survival in human malignant glioma: a randomised, controlled study. Mol Ther. 2004; 10:967–972. [PubMed: 15509514]
6. Ark Therapeutics Ltd withdraws its marketing authorisation application for Cerepro (sitimagene ceradenovec). European Medicines Agency. 2011. [online], http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001103/wapp/Initial_authorisation/human_wapp_000083.jsp&mid=WC0b01ac058001d128
7. Meade T. Primary prevention of ischaemic cardiovascular disorders with antiplatelet agents. Handb Exp Pharmacol. 2012; 210:565–605. [PubMed: 22918747]
8. Wollmann G, Odzuman K, van den Pol AN. Oncolytic virus therapy for glioblastoma multiforme: concepts and candidates. Cancer J. 2012; 18:69–81. [PubMed: 22290260]
9. Curtin JF, et al. HMGB1 mediates endogenous TLR2 activation and brain tumor regression. PLoS Med. 2009; 6:e10. [PubMed: 19143470]