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

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Summary

Background Besides the use of temozolomide and radiotherapy for patients with favourable methylation status, little progress has been made in the treatment of adult glioblastoma. Local control of the disease by complete removal increases time to progression and survival. We assessed the efficacy and safety of a locally applied adenovirus-mediated gene therapy with a prodrug converting enzyme (herpes-simplex-virus thymidine kinase; sitimagene ceradenovec) followed by intravenous ganciclovir in patients with newly diagnosed resectable glioblastoma.

Methods For this international, open-label, randomised, parallel group multicentre phase 3 clinical trial, we recruited patients from 38 sites in Europe. Patients were eligible if they were aged 18–70 years, had newly diagnosed supratentorial glioblastoma multiforme amenable to complete resection, and had a Karnofsky score of 70 or more at screening. We used a computer-generated randomisation sequence to allocate patients in a one-to-one ratio (with block sizes of four) to receive either surgical resection of the tumour and intraoperative perilesional injection of sitimagene ceradenovec (1×10^{12} viral particles) followed by ganciclovir (postoperatively, 5 mg/kg intravenously twice a day) in addition to standard care or resection and standard care alone. Temozolomide, not being standard in all participating countries at the time of the study, was allowed at the discretion of the treating physician. The primary endpoint was a composite of time to death or re-intervention, adjusted for temozolamide use, assessed by intention-to-treat (ITT) analysis. This trial is registered with EudraCT, number 2004-000464-28.

Findings Between Nov 3, 2005, and April 16, 2007, 250 patients were recruited and randomly allocated: 124 to the experimental group and 126 to the standard care group, of whom 119 and 117 patients, respectively, were included in the ITT analyses. Median time to death or re-intervention was longer in the experimental group (308 days, 95% CI 283–373) than in the control group (268 days, 210–313; hazard ratio [HR] 1·53, 95% CI 1·13–2·07; p=0·006). In a subgroup of patients with non-methylated *MGMT*, the HR was 1·72 (95% CI 1·15–2·56; p=0·008). However, there was no difference between groups in terms of overall survival (median 497 days, 95% CI 369–574 for the experimental group *vs* 452 days, 95% CI 437–558 for the control group; HR 1·18, 95% CI 0·86–1·61, p=0·31). More patients in the experimental group had one or more treatment-related adverse events those in the control group (88 [71%] *vs* 51 [43%]). The most common grade 3–4 adverse events were hemiparesis (eight in the experimental group *vs* three in the control group) and aphasia (six *vs* two).

Interpretation Our findings suggest that use of sitimagene ceradenovec and ganciclovir after resection can increase time to death or re-intervention in patients with newly diagnosed supratentorial glioblastoma multiforme, although the intervention did not improve overall survival. Locally delivered gene therapy for glioblastoma should be further developed, especially for patients who are unlikely to respond to standard chemotherapy.

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Introduction

Gliomas are the most common type of primary brain tumour, and more than half are malignant. Despite multimodal therapy with surgery, radiotherapy, and chemotherapy, the prognosis of patients with malignant gliomas is poor, with an average post-operation survival for patients with glioblastoma of just over 1 year.[1] Because a positive association exists between survival and local control achieved by radiologically complete resection,[2,3] improvement of local control after resection should improve outcomes for patients with glioblastoma.[4]

Glioblastoma invariably recurs because of the invasive properties of the cells,[5] warranting treatment of the peritumoral invasive zone. Carmustine wafers are the only approved local intracavity therapy;[6] other approaches—as yet unsuccessful—have included convection-enhanced delivery with toxin conjugates[7] and gene therapy with retrovirus packaging cells

transducing the gene for a prodrug-converting enzyme, herpes-simplex-virus thymidine kinase (HSV-tk).[8]

Local therapies that can be applied during surgery are ideal to bridge the therapeutic gap between surgery and the onset of adjuvant radiochemotherapy. To add to the armamentarium of local therapies, gene therapy was re-assessed with an improved agent. Using an adenoviral vector with high titre, adenovirus-mediated *HSVtk* gene therapy administered locally, intraoperatively, and in conjunction with subsequent intravenous ganciclovir has been developed for the treatment of operable high-grade glioma. The active agent, sitimagene ceradenovec (Ark Therapeutics Ltd, London, UK) is a first-generation replication-deficient adenovirus (serotype 5 with E1 and partial E3 deletions) containing the cDNA for *HSV-tk*. Transgene-expressing cells produce thymidine kinase, which phosphorylates ganciclovir to ganciclovir triphosphate, a cytotoxic nucleotide analogue that selectively kills dividing cells by being incorporated into DNA and leads to apoptosis both in transduced cells and adjacent dividing cells through a so-called bystander effect.[9–11] This process spares normal neurons because they do not proliferate and are therefore not susceptible to the toxic effects of ganciclovir metabolites.[12,13]

In the first two phase 2 studies using the adenovirus-mediated *HSV-tk*, optimal dose (1×10^{12} viral particles) and transduction efficiency were established,[14,15] and multiple small injections covering as much as possible of the surface area of the tumour cavity were shown to be needed to maximise the treatment effect. In a subsequent randomised, controlled phase 2 trial, the safety and efficacy of the treatment were established by showing improved survival as defined by time to death or surgery for recurrence.[16] Consequently, we did a randomised, open-label, parallel group, multicentre phase 3 trial to investigate the efficacy and safety of sitimagene ceradenovec with subsequent ganciclovir for the treatment of operable, newly diagnosed glioblastoma compared with standard treatment.

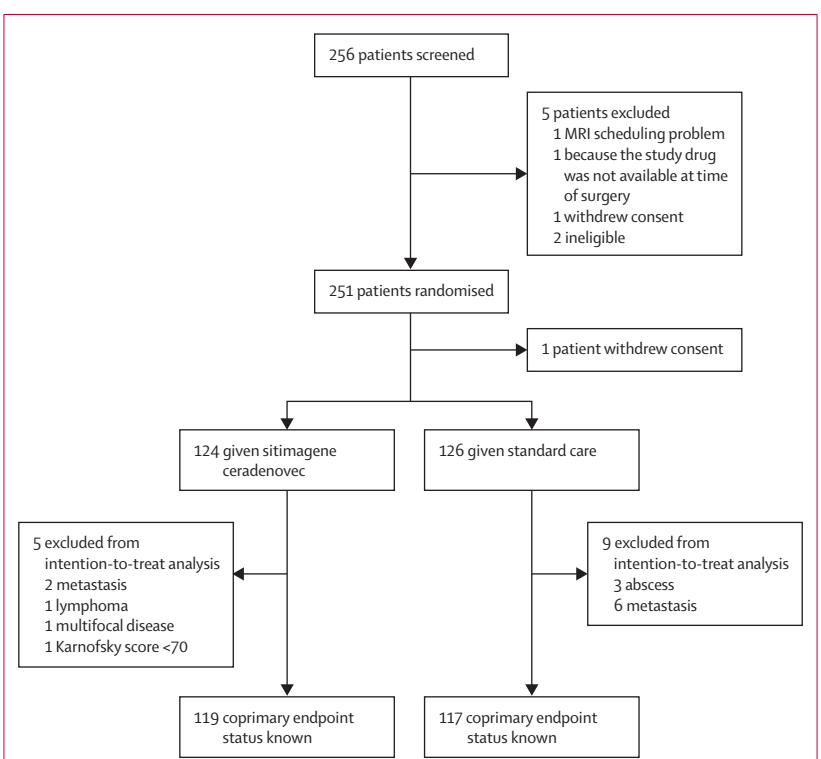

Figure 1: **Trial profile**

Methods

Patients

We recruited adult patients (aged 18–70 years) with a Karnofsky score of 70 or more at screening and newly diagnosed supratentorial glioblastoma multiforme that were deemed by the treating neurosurgeon to be amenable to complete resection from 38 sites in nine countries in Europe. Patients with bihemispheric or multifocal tumours, recurrent glioma, other clinically significant concomitant disease (including renal or liver disease), hypersensitivity to ganciclovir, or patients who had received chemotherapy within 6 weeks of randomisation were excluded from the study.

The protocol was approved by local independent ethics committees and all participants gave written informed consent before any trial-related procedure was done. The trial was done in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

The study was approved by the regulatory authorities in each of the participating countries and by the respective institutional review boards or local ethical committees of the participating centres with the leading institution being the Ethikkommission der Ärztekammer (Hamburg, Germany).

Randomisation and masking

The randomisation sequence was generated centrally by Covance Laboratories (Harrogate, UK) using a computerised interactive voice response system. Randomisation was done within 24 h of planned surgery by the investigator telephoning the computerised interactive voice response system, which then automatically allocated patients to study treatment. Patients were randomised in a one-to-one ratio to experimental or control group in blocks of four. The block size was not stratified by site or region because we thought small numbers of patients would be recruited by individual sites (and in the early stage of recruitment from a single centre within a country), and because in an open-label study such blocking might disclose the random assignment of patients at the end of a block. Neither the patients nor investigators were masked to treatment during the course of the study.

Procedures

The *HSV-tk* cDNA was cloned under a cytomegalovirus promoter and the structure verified by sequencing.