Suicide gene therapy for recurrent glioblastoma

- Combination of microRNA and suicide gene for targeting Glioblastoma: Inducing apoptosis and significantly suppressing tumor growth in vivo
- The potential of mesenchymal stem cell coexpressing cytosine deaminase and secretory IL18-FC chimeric cytokine in suppressing glioblastoma recurrence
- Suicide gene therapy using allogeneic adipose tissue-derived mesenchymal stem cell gene delivery vehicles in recurrent glioblastoma multiforme: a first-in-human, dose-escalation, phase I clinical trial
- Case report: Stem cell-based suicide gene therapy mediated by the herpes simplex virus thymidine kinase gene reduces tumor progression in multifocal glioblastoma
- Non-coding RNAs enhance the apoptosis efficacy of therapeutic agents used for the treatment of glioblastoma multiform
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Suicide gene therapy has been explored as a potential treatment approach for recurrent glioblastoma, a type of aggressive brain tumor. One of the strategies employed is the use of the herpes simplex virus thymidine kinase (HSV-TK) gene.

In this approach, the HSV-TK gene is introduced into glioblastoma cells either directly or through the use of viral vectors. Once the gene is present in the cells, an inactive prodrug called ganciclovir is administered. The HSV-TK enzyme produced by the gene then converts the prodrug into a toxic compound, leading to the death of the cancer cells.

The concept behind this therapy is to selectively target and kill glioblastoma cells while sparing healthy brain tissue. However, it is important to note that the effectiveness of suicide gene therapy for recurrent glioblastoma remains an area of active research, and results have varied across studies.

Clinical trials have been conducted to assess the safety and efficacy of suicide gene therapy in glioblastoma patients. While some trials have shown promising results, demonstrating tumor size reduction and increased survival rates, others have reported limited therapeutic benefits.

It is worth mentioning that suicide gene therapy for recurrent glioblastoma is still considered an experimental treatment, and its availability may be limited to clinical trials or specialized medical centers.

An investigation aimed to evaluate the safety of suicide gene therapy using allogeneic adipose tissue-derived mesenchymal stem cells (ADSCs) carrying herpes simplex virus thymidine kinase gene for the first time in patients for glioblastoma recurrence treatment.

This study was a first-in-human trial, open-label trial, single-arm trial, phase 1 trial with a classic dose escalation 3 + 3 design. Patients who did not undergo surgery for their recurrence were included and

received this gene therapy protocol. Patients received the intratumoral stereotactic injection of ADSCs according to the assigned dose followed by prodrug administration for 14 days. The first dosing cohort (n = 3) received 2.5 × 105 ADSCs; the second dosing cohort (n = 3) received 5 × 105 ADSCs; the third dosing cohort (n = 6) received 10 × 105 ADSCs. The primary outcome measure was the safety profile of the intervention.

A total of 12 patients with recurrent GBM were recruited. The median follow-up was 16 (IQR, 14-18.5) months. This gene therapy protocol was safe and well tolerated. During the study period, eleven (91.7%) patients showed tumor progression, and nine (75.0%) died. The median overall survival (OS) was 16.0 months (95% CI 14.3-17.7) and the median progression-free survival (PFS) was 11.0 months (95% CI 8.3-13.7). A total of 8 and 4 patients showed partial response and stable disease, respectively. Moreover, significant changes were observed in volumetric analysis, peripheral blood cell counts, and cytokine profile.

The present clinical trial, for the first time, showed that suicide gene therapy using allogeneic ADSCs carrying the HSV-TK gene is safe in patients with recurrent GBM. Future phase II/III clinical trials with multiple arms are warranted to validate our findings and further investigate the efficacy of this protocol compared with standard therapy alone.

Trial registration: Iranian Registry of Clinical Trials (IRCT), IRCT20200502047277N2. Registered 8 October 2020, https://www.irct.ir/ [1)]

A 37-year-old man presented with two evident foci of glioblastoma at the left frontal and left parietal lobes. The patient received an injection of bone marrow-derived MSCs delivering the herpes simplex virus thymidine kinase (HSV-tk) gene to the frontal focus of the tumor, followed by ganciclovir administration as a prodrug for 14 days. For follow-up, the patient was periodically assessed using magnetic resonance imaging (MRI). The growth and recurrence patterns of the foci were assessed. After the injection on 09 February 2019, the patient's follow-up appointment on 19 December 2019 MRI revealed a recurrence of parietal focus. However, the frontal focus had a slight and unremarkable enhancement. On the last follow-up (18 March 2020), the left frontal focus had no prominent recurrence; however, the size of the left parietal focus increased and extended to the contralateral hemisphere through the corpus callosum. Eventually, the patient passed away on 16 July 2020 (progression-free survival (PFS) = 293 days, overall survival (OS) = 513 days).

The gliomatous focus (frontal) treated with bone marrow-derived MSCs carrying the HSV-TK gene had a different pattern of growth and recurrence compared with the non-treated one (parietal).

Trial registration: IRCT20200502047277N2. Registered 10 May 2020-Retrospectively registered, https://eng.irct.ir/trial/48110 [2)]

1)
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