Comparison of CAR-T Cell Therapy Generations for the Treatment of Glioblastoma

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Abstract

This study analyzed bioluminescent data from xenograft mouse models of glioblastoma in order to compare the effectiveness between 2nd- and 3rd-generation CAR-T cells in reducing tumor volume. Results suggested that 3rd-generation CAR-T cells were more effective than 2nd-generation CAR-T cell treatments in these preclinical models.

Introduction

Glioblastoma

Glioblastoma multiforme (GBM), also called glioblastoma, is the most common and aggressive type of malignant glioma, or brain and spinal cord tumor. Gliomas represent 80% of all malignant primary brain tumors in adults. Once affected, patients experience a poor prognosis and quality of life due to severe symptoms. At best, they can receive symptom control through drug treatments that mostly alleviate pain.

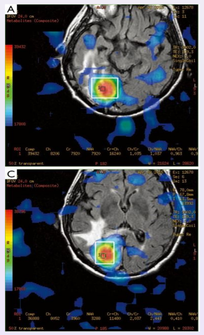


Figure 1. Imaging of an area of interest, denoting a possible glioblastoma tumor in colored area

CAR-T cell therapy

CAR-T cell therapy is a form of immunotherapy that uses engineered T-cells to target and attack tumor cells by obtaining cells and adding a recombinant receptor called a chimeric antigen receptor (CAR).

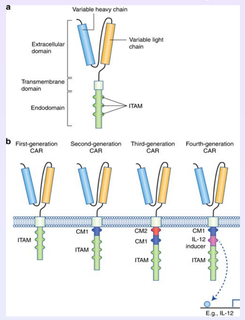


Figure 2. Comparison of CAR structures for each generation, beginning with core structure

CAR-T cell therapy has undergone much development, beginning with the first-generation CARs. Next, second-generation and third-generation CAR-T cells have added co-stimulatory domains. Thus, they allow the newly engineered T-cells to induce full T-cell activation, target killing, and long-term persistence. Although they perform much better than first-generation CARs, there is still room to improve.

Hypotheses

Alternative Hypothesis

Considering that newer generation CAR-T cells have a greater number of co-stimulatory domains, newer generation CAR-T cells are hypothesized to perform significantly better than past generations in reducing GBM tumor volume.

Null Hypothesis

There is no difference between the different CAR-T cell generations in reducing GBM tumor volume. This would suggest that the added co-stimulatory domains have little to no effect in improving the antitumor response.

Methodology

The statistical analysis focused on full-text research involving xenograft animal models specifically discussing antigen expression and tumor size reduction. Systematic reviews, meta-analyses, clinical trials, and in vitro studies were utilized as a reference.

Data were collected by obtaining quantitative bioluminescence data from studies analyzing tumor reduction due to CAR-T cell therapy. To standardize the units, bioluminescence data was taken and calculated using the following formula for %T/C:

$$\%T/C = 100 \times T/\Delta C \text{ if } \Delta T \geq 0$$

$$\%\ \text{Regression} = 100 \times T/\text{TInitial if } \Delta T < 0$$

T=Tumor volumes of UTD/CAR-T group on final day
Tinitial= Tumor volumes of UTD/CAR-T group on initial day
ΔT = T - Tinitial

C = Mean tumor volume of PBS control group on final day
ΔC = Mean tumor volume of PBS control group difference between final and initial days

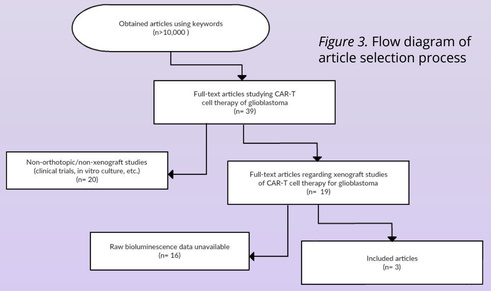
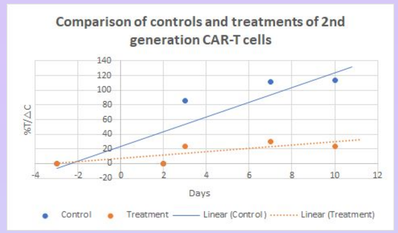
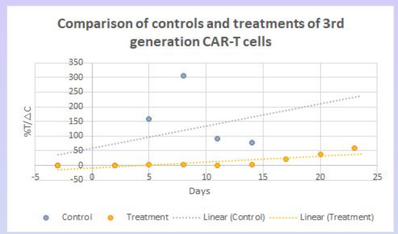


Figure 3. Flow diagram of article selection process

Results





The slope of %T/ΔC against time was calculated for the control and 2nd-generation CAR-T cell treatment. Both lines showed a positive slope, but the control group had a constant higher %T/ΔC value than the treatment group. A t-test comparing the treatment and control on day 10 suggested that the lower values of the 2nd-generation CAR-T cell treatment group in comparison with the control group were likely statistically significant ($p = 0.003$).

This process was repeated using data from 3rd-generation CAR-T cells, which yielded slopes for the control treatment. Both lines also showed a positive slope, and the control group had a consistently higher %T/ΔC value than the treatment group. The t-test comparing treatment and control on day 11 suggested that lower values of the 3rd-generation CAR-T cell treatment were likely statistically significant ($p = 0.004$).

Finally, a one-tailed two-sample T-test was run between the %T/ΔC of the day 10 2nd-generation CAR-T cell treatment and the day 11 3rd-generation CAR-T cell treatment. The p-value obtained suggested that the 3rd-generation CAR-T cell treatment had significantly more tumor reduction than that of the 2nd-generation CAR-T cells ($p= 0.005$).

Discussion

By looking at the average BLI and %T/ΔC values, it is apparent that both treatments had greater performance than their respective controls. There are several distinctions that suggest a greater antitumor response in the 3rd-generation CAR-T cell treatment.

Firstly, the 3rd-generation treatment group mice survived much longer than any of the controls or treatments within both studies. Since both studies used the same criteria for euthanization, this meant that mice in the treatment group had the least harm from tumor burden in comparison with other groups of mice.

Additionally, 3rd-generation CAR-T cell treatment had a lower %T/ΔC value on day 11 than that of the 2nd-generation CAR-T treatment. After conducting a t-test to determine significance in tumor reduction, the difference was found to be statistically significant ($p= 0.005$). As a result, it suggests that the 3rd-generation CAR-T cells are effective in preclinical models, which could potentially be extrapolated into clinical models.

Further Work

This paper only discussed the efficacy of CAR-T cell treatment in a preclinical setting. In the future, it will be beneficial to observe the patterns in clinical trials, to investigate possible off-target toxicities. Currently, there are a few clinical trials that have been conducted for treating GBM with CAR-T cells, but they demonstrated a recurrence of some sort after treatment.

It may also be beneficial to investigate the efficacy of different target antigen receptors to improve not only CAR-T cells but other forms of immunotherapy as well. By targeting an antigen that is expressed on a large proportion of tumor cells, it lowers the chances of tumor recurrence.

Acknowledgements

I would like to thank:

- Dr. Zev Binder, M.D., Ph.D.
- Dr. Paul Jeng, Ph.D.
- Dr. Mitchell Ho, Ph. D.
- Dr. Madeline B. Torres, M.D.
- Dr. Nikki Malhotra

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