REPORT
25th SOCIAL RETURN OF THE RESEARCH
CANCER

THERAPIES AND SPECIFIC BIOMARKERS OF THE ORGANS TO IMPROVE TREATMENT OF CEREBRAL METASTASIS

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1. Project Summary

Brain metastasis, a serious complication of cancer where cancer cells spread to the brain, poses a significant challenge in oncological care. Currently, available treatments such as radiotherapy and surgery offer unsatisfactory results, with patients facing a bleak prognosis, often with a life expectancy of less than a year. Recent research has revealed that cancer cells can transform normal brain cells, called astrocytes, by activating a specific molecule called STAT3. Inhibiting this molecule has shown to reduce both the number and size of brain metastases in animal models and experimentally treated patients.

To address this problem, our project proposed an ambitious research plan focusing on three main objectives. Firstly, understanding the interaction between non-cancerous and cancerous cells in the brain to identify new therapeutic targets. Secondly, using this knowledge to improve the efficacy of available therapies such as radiotherapy and immunotherapy, and exploring the possibility of reducing their side effects. Thirdly, transferring findings from experimental models to patients, using non-invasive biopsies (blood or cerebrospinal fluid samples) to inform on the status of the interaction between cancerous and non-cancerous cells in the brain.

This collaborative research project was conducted in three prestigious research centers, combining the expertise of basic and clinical researchers. It was expected that the results obtained would provide the basis for designing new clinical trials to develop more effective and precise treatments against brain metastasis, offering hope to patients affected by this devastating disease.

2. Results Obtained

S100A9 has been identified as a liquid biopsy biomarker (in blood) to personalize the use of radiotherapy in brain metastasis, as the presence of this molecule confers radioresistance in patients treated with radiotherapy for brain metastases. Currently, this potential biomarker is being studied in a prospective multicenter clinical study in Spain for clinical validation.

A panel of cytokines predicting the occurrence of radionecrosis has been identified, which could help predict those patients who may have a higher risk of toxicity from cerebral radiotherapy, which remains one of the most used treatments for local control of brain metastases.

A method was also established to evaluate biomarkers in samples of brain metastases, identifying TIMP1 as the first liquid biopsy biomarker to select patients who will respond to immunotherapy.

The discoveries made during the project also include the justification for a clinical trial using silibinin, a natural flavonoid present in milk thistle, which has activity as a pSTAT3 inhibitor, as a complementary treatment to control brain metastases, combined with anti-PD-1 and anti-CTLA4 antibodies (immunotherapy) (results pending publication).

3. Relevance with Possible Future Implications

The results obtained have several potential practical applications. Firstly, the S100A9 biomarker could help identify patients who are more radioresistant and who would obtain less benefit from radiotherapy for brain metastases. This biomarker is being explored to identify patients who will respond to the drug azeliragon in an ongoing clinical trial.

Circulating CD74+ macrophages could be a new biomarker to assess the prognosis of brain metastasis, and the transcriptional signature of CD74+ macrophages/microglia could provide new biomarkers for various brain disorders, including tumor processes, neurodegenerative, and neuroinflammatory disorders.

The ability to predict the occurrence of radionecrosis could have a significant impact on the treatment of patients with brain metastases, allowing early treatment and differentiation between radionecrosis and tumor progression, which is crucial for determining the appropriate course of action.

The ability of silibinin to act against brain metastases through the inhibition of reactive STAT3 astrocytes is being studied in a clinical trial to prevent relapse after brain surgery, and our results also justify conducting combination clinical trials with immunotherapy (anti-PD-1/PD-L1 and anti-CTLA4 antibodies) to increase the effectiveness of cancer treatments.

4. Generated Scientific Bibliography

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