Cancer is the second leading cause of human death worldwide, accounting for one in every six deaths. Cancer is the subject of intense clinical research into treatments and potential cures. There are many forms of serious cancer, but one of the most difficult to treat is Glioblastoma Multiforme (GBM). There is a need for improved treatments for GBM patients, like the inclusion of first-line immunotherapy to fight their cancers. Meta-analysis (that is, the examination of data from many independent studies, to help determine overall trends) have investigated the effectiveness of specific immunotherapy treatment for GBM. These studies show that immunotherapy can cause a significant increase in survival time. However, no single research group has successfully demonstrated the efficacy of this type of treatment in a randomised controlled trial (RCT).

**WHAT MAKES GBM SO SERIOUS?**

Brain tumours are the leading causes of cancer deaths in males aged 20–39 and the fourth most common cause in females of the same age. However, GBM is a particularly dangerous form of cancer, and the most frequent malignant brain cancer in adults. It is a rapidly growing tumour of the brain and spinal cord, which causes symptoms to progress swiftly. The years of loss of life due to GBM is the highest of all cancers, in part due to its occurrence at a young age and its poor prognosis. Despite this, GBM is referred to as an orphan disease as it is rare and has not had major interest from drug companies in developing a treatment. The current standard-of-care following diagnosis of GBM includes neurosurgery, radiotherapy, and maintenance chemotherapy. Unfortunately, however, these treatments do not fully control the disease, which contributes to its poor prognosis.

**TREATING GBM WITH IMMUNOTHERAPY**

Unfortunately, the available options for treating people with GBM have not changed in recent years. However, research has been carried out into innovative new areas of treatment including tumour-treating fields, anti-angiogenic treatments, targeted therapies, oncolytic virus therapy, and immunotherapies. One example of a targeted immunotherapy is dendritic cell (DC) vaccines. Dendritic cells help the immune system to recognise and attack abnormal cells, such as cancer cells. To make the vaccine, scientists grow dendritic cells alongside cancer-specific antigens in the lab. The vaccine then stimulates the patient’s own immune system to attack the cancer. In a clinical context, RCTs are used to compare the effects of different drugs, medical devices, surgical techniques, diagnostics procedures, or other medical treatments. Individuals enlisted in RCTs are different from one another in both known and unknown ways. These differences can’t be directly controlled, but they can influence study outcomes. By randomly allocating people between the treatments being compared, an RCT offers researchers statistical control over these influences. RCTs are considered to be the most reliable form of scientific verification in the hierarchy of evidence that influences healthcare policy and practice, because they reduce spurious causality and bias. In some areas, great progress has been made through RCTs. These trials tend to work by comparing a new experimental treatment against the best current treatment as a control. However, RCTs can be expensive. They often take many years to complete and it can be difficult to reach the very large sample sizes needed to yield significant results. Due to the costs of running RCTs, they can’t always test every variable and give the full picture of complicated medical situations.

**WHY HAVE RCTS BEEN INEFFECTIVE FOR STUDYING GBM IMMUNOTHERAPIES?**

Professor Van Gool carried out a review of the literature around how good RCTs are at assessing the efficacy of immunotherapy. He concluded that there are many reasons why carrying them out can be problematic.

Firstly, the design of an RCT can be a major challenge. It can be hard to find an appropriately matched control group when you have to include variables such as the clinical status of the patient, the tumour biology, and chemosensitivity (MGMT promoter methylation status) of the disease, which contributes to its poor prognosis.
Behind the Research

Professor Stefaan Van Gool

The Immu-No-Kologische Zentrum Köln

Research Objectives

The Immuno-Oncological Center (IOZK), a private non-profit organisation in Cologne, delivers individualised multimodal immunotherapy for cancer patients.

Detail

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IOZK, Hohenstuhlenring 30–32
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Bio

Stefaan Van Gool, MD, PhD, is a paediatric neuro-oncologist. After his studies in Leuven and Münster, he became Professor and successfully established dendritic cell vaccination for brain cancer in Europe. In 2015 he became Medical Director at the Immuno-Oncological Center Köln where he delivers individualised multimodal immunotherapy for cancer patients.

References


Personal Response

How close are we to bringing multimodal immunotherapy into routine practice for GBM patients?

Clincially and technically, I would say ‘very close’. The treatment is ambulant and does not add any major toxicity. Patients can be referred to a few specialised centres in each country where this part of the treatment can be administered, in close communication with the local oncology centre. The HGG-IMMUNO-Group brought neuro-oncologists from many countries together to build up a network within Europe for delivering DC vaccination. However, at the regulatory and health insurance level, I have to say ‘very far’. All must work together to pass these hurdles, with the goal of prolonging life, and good quality of life, for patients with GBM.

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Retrofittumours, the tumour-host interaction, and the systemic immunity. Second, people’s reactions vary in response to radiochemotherapy. This can influence the immune system and the potential transient clinical need of steroids during treatment, and in turn affect to a large extent how long a patient is able to stick to a study protocol.

Thirdly, the highly dynamic character of the tumour and the micro- and macro-environment is not very compatible with a fixed-treatment protocol within an RCT.

Fourth, there are ethical issues related to the control group for an RCT for GBM, as prolonging overall survival is in question. And finally, reality shows that the combination of laboratory testing regulations (such as GLP, GTP, GMP, and GCP) may play a part, and pose a significant hurdle for academic centres as well as the pharmaceutical industry.

WHAT DID THE LITERATURE STUDY CONCLUDE?

The researchers concluded that GBM treatment is affected by a number of variables: the complexity of the tumour, the complexity of the immune and inflammatory micro-environment, and the complexity of combined treatment approaches. It is also impacted by the complexity of dynamic changes occurring within the tumour, the tumour micro-environment, and the immune system. This means it’s very challenging and expensive to create an appropriate control group for GBM patients within an RCT.

THE FUTURE OF GBM TREATMENT

Notably, Professor Van Gool’s retrospective analysis of 70 GBM patients revealed that a combination of first-line treatments in addition to immunotherapy strategies resulted in a positive synergistic effect. These combination strategies demonstrated a highly significant improvement in overall survival. Professor Van Gool explains this innovative concept: ‘Neurosurgery, radiotherapy, chemotherapy, targeted (immune) therapies, and immunogenic cell death therapies are all anti-cancer strategies that might partly induce anti-cancer immunity and prolong patient survival. In most cases, however, this is not enough, and active specific immunotherapy is needed for the installation of anti-cancer immunity. Finally, modulatory immunotherapy (like checkpoint inhibitors) might be needed to facilitate the actively induced anti-cancer immune response.’ The philosophy is that immunotherapy strengthens and activates the patient’s own defence system, to help fight their cancer. This protective immunotherapy is needed for the patient to survive. In most cases, however, anticancer immunity and prolong survival. Professor Van Gool explains this innovative concept: ‘Neurosurgery, radiotherapy, chemotherapy, targeted (immune) therapies, and immunogenic cell death therapies are all anti-cancer strategies that might partly induce anti-cancer immunity and prolong patient survival. In most cases, however, this is not enough, and active specific immunotherapy is needed for the installation of anti-cancer immunity. Finally, modulatory immunotherapy (like checkpoint inhibitors) might be needed to facilitate the actively induced anti-cancer immune response.’ The philosophy is that immunotherapy strengthens and activates the patient’s own defence system, to help fight their cancer. This protective immunotherapy is needed for the patient to survive. In most cases, however, anticancer immunity and prolong survival.

A combination of first-line treatments in addition to immunotherapy strategies resulted in a positive synergistic effect.

The Induction of Immunogenic Cell Death (ICD) During Maintenance Chemotherapy and Subsequent Multimodal Immunotherapy for Glioblastoma (GBM). Austin Oncol Case Rep, 3(1), 1010

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