Pol Merkur Lek, 2023; LI, 4: 430-432

SHORT COMMUNICATION

DOI: 10.36740/Merkur202304119

A NEW HYPOTHESIS IN THE TREATMENT OF RECURRENT GLIOBLASTOMA MULTIFORME (GBM). PART 1: INTRODUCTION

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ABSTRACT

Modern treatment of glioblastoma multiforme (GBM) is based on neurosurgical methods combined with radiotherapy and chemotherapy. The prognosis for patients with GBM is extremely poor. Often, complete removal of the tumor is impossible and it often recurs. Therefore, in addition to standard regimens, modern methods such as modulated electrohyperthermia, monoclonal antibodies and individualised multimodal immunotherapy (IMI) based on vaccines and oncolytic viruses are also used in the treatment of GBM. Radioiodine therapy (RIT) also holds out hope for an effective treatment of this extremely aggressive brain tumor. The expression of the sodium iodide symporter (NIS) gene has been proven to have a positive effect on the treatment of selected cancers. Research confirm the presence of expression of this gene in GBM cells, although only in animal studies. Is it possible and therapeutically effective to treat GBM with RIT without the use of an exogenous NIS gene? The safety of therapy is relevant, as the only more serious adverse effect may be hypothyroidism. The use of RIT requires further clinical studies in patients. Perhaps it is worth revolutionizing GBM therapy to give sufferers a "new life".

KEY WORDS: glioblastoma multiforme, sodium iodide symporter (NIS), radioiodine therapy (RIT), tumor, oncology

Contemporary treatment methods for glioblastoma multiforme (GBM) involve neurosurgical techniques combined with radiotherapy and chemotherapy. Considering the findings of previous laboratory studies, which indicate that the expression of the sodium iodide symporter (NIS) gene has a positive impact on the treatment of certain cancers, the following question arises: Is it possible to treat GBM solely with radioiodine therapy (RIT)? It is highly probable that NIS exhibits activity in GBM cells. Therefore, it seems that administering RIT through NIS could inhibit the progression of GBM. Who knows, then, whether NIS will act favorably through RIT and impede the progression of GBM? The sodium iodide symporter, also known as the NIS protein, is responsible for the uptake of iodide ions into the cell and plays a fundamental role in thyroid gland function. Previous studies on the sodium iodide symporter include, among others, demonstrating the expression of the NIS protein in thyrocytes and tissues of other organs, investigating the antigenicity of the symporter in autoimmune thyroid diseases, and uncovering the genetic factors influencing the diverse activity of the NIS protein. Notably, the expression of NIS has been detected not only in the thyroid but particularly in various tumor cells [1-6]. Hence, the question arises whether it is possible and therapeutically effective to utilize the NIS pathway for targeted GBM treatment.

The administration of RIT is entirely safe, with the only potential complication being thyroid dysfunction depending on the dosage. Indeed, recent studies have demonstrated that, for thyroid cancer, the maximum RIT dose is 37,000 MBq (1,000 mCi) [7-8]. This raises the question of whether it is worth considering the use of ablative RIT at a dosage of 740 MBq (20 mCi) for GBM in an outpatient setting with the possibility of repeat administration.

What do we have to lose? After all, patients with GBM have a very short lifespan, and the prognosis is exceptionally unfavorable. However, the observation of NIS gene expression has been identified in GBM, albeit only in animal laboratory studies [9]. Perhaps it is worth starting to practice and confirming the effectiveness of RIT in GBM therapy, as suggested by numerous scientific indicators.

As early as 1955, Amyes et al. localized brain tumors using radioactive iodine and phosphorus [9]. In this procedure, a needle probe was first employed, proving to be highly useful in swiftly locating and determining the affected area of the brain tumor.

Radioisotopes of various elements are increasingly being used in nuclear medicine. Herein lies the potential efficacy of beta radiation, such as RIT, beyond its imaging capabilities. Currently, the experimental NIS gene is being employed,

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but due to time constraints, it may be worth considering the prompt administration of RIT in GBM, at doses ranging from 740 MBq (20 mCi) to as high as 5550 MBq (150 mCi). It has been demonstrated that, among other applications, RIT accumulates up to 37,000 MBq (1,000 mCi) in thyroid tumors [10-11]. This further substantiates the notion that the use of RIT does not have a negative impact on healthy cells in the body; it may only result in thyroid dysfunction, as mentioned before. It is also worth noting that the radioactive iodine activity utilized in the treatment of multinodular toxic goiter is approximately 150-200 μCi/g of thyroid tissue, calculated using the formula: thyroid mass (g) x 150-200 μCi x 1/T24 iodine uptake at 24 hours. RIT can be administered in higher doses - ranging from 370 MBq (10 mCi) to 740 MBq (20 mCi) - in outpatient settings for conditions such as hyperthyroidism in Graves' disease or toxic multinodular goiter [12].

Complete removal of Grade IV GBM is not always feasible. Therefore, in accordance with the current motivation, in addition to the aforementioned standard therapies, namely neurosurgery [13], conventional radiotherapy [14], chemotherapy (e.g., temozolomide), modulated electro-hyperthermia (mEHT) [15-16], and administration of humanized monoclonal antibodies (e.g., pembrolizumab), the use of RIT [17-19] can be considered. Attention has also been drawn to targeted therapy utilizing tyrosine kinase inhibitors (imatinib, sunitinib, and sorafenib), as well as the application of novel drugs such as crizotinib, entrectinib, or larotrectinib [20-23]. NanoTherm® therapy is employed in patients with GBM who have exhausted conventional treatment methods [24]. Recently, personalized multimodal immunotherapy (IMI) based on anti-cancer vaccines [25-31] and oncolytic viruses [12, 32-33] has been developed.

It may be worthwhile to make efforts today and attempt to revolutionize the existing therapy through RIT, even without the genetic aspects of NIS, but in its classical form - just as before. What is extremely significant is that this therapy can be entirely cost-free, and even if there are charges involved, they do not have to be exorbitant. The only consequence would be thyroid dysfunction, which is merely a "complication." However, could we potentially gain a "new lease on life" as patients are liberated from GBM?

Similarly, RIT has been and continues to be used, drawing inspiration from the publications of Hermida et al. and Gursoy et al., in patients with amiodarone-induced thyrotoxicosis (AIT) with very low radioiodine uptake (RAIU) [34-37]. However, the authors of the study utilized very high activities of radioactive iodine (up to 2,960 MBq [80 mCi]), which are not routinely employed in the treatment of hyperthyroidism. No severe adverse effects were observed in patients following RIT therapy for AIT. They only experienced thyroid dysfunction [34-35]. In the course of AIT treatment, when antithyroid drugs (ATDs), including thionamide derivatives such as propylthiouracil (PTU) and imidazoles (MMI, tiamazole, Metizol), led to agranulocytosis, hepatitis, vasculitis, or lupus-like syndrome, the use of RIT became necessary [38-40].

Again, the authors of this discussion suggest that the use of RIT in personalized treatment for GBM can be an effective complement to other therapies, just as the use of RIT in AIT [34-35, 40]. This therapy can play a crucial role in cases of GBM recurrence. However, current clinical studies in humans are lacking, although positive results have been achieved in Wistar rats and mice through the combination of NIS gene therapy and RIT [41].

The application of RIT in patients with recurrent GBM appears to be a promising therapeutic option. The authors speculate that this will provide a completely new perspective within the treatment paradiGBM.

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CONFLICT OF INTEREST

The Authors declare no conflicts of interest.

RECEIVED: 05.04.2023
ACCEPTED: 05.06.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.