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Standard therapy or additionally radioactive iodine (^{131}I) therapy; which will stop the recurrence of glioblastoma multiforme (GBM)?

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive malignant brain tumour. The average survival time for a patient diagnosed with GBM, using standard treatment methods, is several months. Authors of the article pose a direct question: Is it possible to treat GBM solely with radioactive iodine (^{131}I) therapy without employing the sodium iodide symporter (NIS) gene? After all, NIS has been detected not only in the thyroid but also in various tumours. The main author of this article (A.C.), with the assistance of her colleagues (physicians and pharmacologists), underwent ^{131}I therapy after prior iodine inhibition, resulting in approximately 30% reduction in tumour size as revealed by magnetic resonance imaging (MRI).

Classical therapy for GBM encompasses neurosurgery, conventional radiotherapy, and chemotherapy (e.g. temozolomide). Currently, tyrosine kinase inhibitors (imatinib, sunitinib, and sorafenib) are being used. Additionally, novel drugs such as crizotinib, entrectinib, or larotrectinib are being applied. Recently, personalised multimodal immunotherapy (IMI) based on anti-tumour vaccines derived from oncolytic viruses has been developed, concomitant with the advancement of cellular and molecular immunology. Thus, ^{131}I therapy has been successfully employed for the first time in the case of GBM recurrence. **(Endokrynol Pol 2024; 75 (2): 130–139)**

Key words: *glioblastoma multiforme (GBM); immunotherapy; chemotherapy; virotherapy; radioactive iodine (^{131}I) therapy; sodium iodide symporter (NIS); gene mutation; cell-free DNA (cfDNA); cancer vaccines; oncolytic viruses*

Introduction

It is well known that the standard therapy for GBM includes neurosurgery, radiotherapy (tomotherapy), and chemotherapy. However, the effectiveness of such treatments is not satisfactory. Undesirable consequences may occur, especially with prolonged administration of temozolomide (TMZ). Consequently, a new form of GBM therapy has been under development for several years. This latest, somewhat revolutionary therapy involves the combination of immunotherapy and virology (oncolytic viruses and anti-tumour vaccines). Immunotherapy also encompasses antibodies acting as immune checkpoint inhibitors, as well as chimeric antigen receptor (CAR) T-cell therapy [1]. The progress in immunotherapy-based anti-tumour therapy can be traced back to the 1970s [2, 3], and contributions by Abbas et al. [4] have led to the advancement of cellular and molecular immunology.

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In 1980, Schirrmacher [5] discovered the interaction between cancer and living cells in the tumour microenvironment (TME), leading to malignant transformation [6, 7]. The tumour creates a shield-like defence, involving both non-immunological and immunological mechanisms [1].

Personalised medicine entails the molecular analysis of tumour properties and targeted therapy using small molecule inhibitors. It comprehensively considers both the tumour and the host in the context of immunotherapy. An example of this approach is individualised multimodal immunotherapy (IMI), which is based on the individuality of tumour-host immune interactions and the concept of immunogenic cell death (ICD) induced by oncolytic viruses (OV) [8].

Standard GBM therapy includes neurosurgical surgery, radiotherapy (tomotherapy), and chemotherapy. The effectiveness of this type of therapy is not so effective, and side effects may occur more than once, especially with chronic TMZ intake; hence, a new form of GBM therapy was started and has been developed for several years. This newest "revolutionary" therapy is immunotherapy combined with virology (oncolytic viruses and cancer vaccines). Immunotherapy also includes checkpoint inhibitor antibodies, chimeric antigen receptor (CAR) T-cells [1]. This advancement in immunotherapy-based cancer therapy continued throughout the 1970s [2, 3], and Abbas et al. [4] contributed to the development of cellular and molecular immunology.

In 1980, Schirrmacher [5] discovered the interaction between cancer and life-cell and the TME, which is the result of malignant transformation [6, 7]. The tumour forms a "shield" as a form of defence by both non-immune and immune mechanisms [1]. Personalised medicine includes molecular analysis of tumour properties and targeted therapy with small molecule inhibitors. Individualised medicine covers the entire patient (tumour and host) in the context of immunotherapy. An example is IMI. It is based on the individuality of immunological tumour-host interactions and on the concept of ICD induced by OV [8].

This article summarises current knowledge about traditional and modern treatment options used in the therapy of GBM. The data are based on a review of all the latest Medline articles from 2022 and 2023 related to GBM therapy. The aim of this publication is to present Radioactive Iodine (^{131}I) therapy as a potential cutting-edge treatment in GBM. We describe the effectiveness of ^{131}I treatment in recurrent GBM, which was confirmed by medical imaging tests and the good general condition of the patient after ^{131}I administration.

Neurosurgical treatment

The term "neurosurgery" was first used in English language in 1904 [9], but the first glioma resection was performed in 1884 by Rickman Godlee [10]. The aim of neurosurgical therapy is to completely remove the tumour mass, which is not always successful, especially in malignant gliomas without a clear margin (border) [11–13].

GBM tumor is surgically removed with the use of oncological fluorescence. Launching this method of intraoperative diagnostics, after implementing the methods of neuromonitoring, intraoperative awakening, or tractography, is another step towards further increasing the effectiveness and safety of these operations. Before the surgery (about 24 hours), the patient receives oral oncological fluorescence (5-aminolevulinic acid, 5-ALA), which uses the unique phenomenon that tumour cells of GBM accumulate contrast. 5-ALA as a precursor to haemoglobin synthesis leads to the accumulation of fluorescent porphyrins [14], and oral administration of 5-ALA leads to the accumulation of protoporphyrin IX (PpIX) in GBM. To sum up, during the procedure, after illuminating the surgical field with light of a specific colour (usually pink/red), the areas covered by the neoplastic infiltrate start to glow automatically. The more intense the staining, the greater the infiltration of the observed area with the tumour [15–17]. This type of therapy (using 5-ALA) is very popular in Europe, but it has not been approved in the United States [15].

Tomotherapy as opposed to classic therapy

Until recently, classical radiotherapy was used [18, 19]. Currently, tomotherapy is used, i.e. a technologically advanced accelerator for irradiation using the image-guided intensity modulated radiation therapy (IG-IMRT) method. This method enables the delivery of a specific and planned dose of radiation to the neoplastic tumour, sparing healthy tissue. IG-IMRT additionally enables treatment adaptation, i.e. changing the treatment plan depending on changing conditions (tissue swelling, tumour volume reduction, patient weight loss) [20].

Modulated electro-hyperthermia

Fiorentini and Szasz [21] worked out in detail the biophysics of modulated electro-hyperthermia (mEHT). mEHT aims to combine heating and the action of electric fields to completely damage the tumour (cancerous tissue). The differences (electrical properties) between the diseased (cancerous) and healthy tissue should be taken into account [21–25]. According to conventional hyperthermia, the dose is measured by

the temperature reached in 90% of the tumour. This requires monitoring with intra-tumour thermometers or magnetic resonance imaging (MRI) [26] technology. Scientific research by Fiorentini and Szasz [21] has shown that doses of mEHT are not measured by the temperature in the tumour, but rather by the energy deposited in the tumour required to produce sensitising and cell-killing effects.

NanoTherm® therapy: a promising method of treating recurrent glioblastoma multiforme

NanoTherm® therapy is a method used in patients with GBM when classical methods of treatment have been exhausted. This innovation is based on the combination of thermal ablation and nanotechnology. A specially developed and patented ferrofluid, containing magnetic nanoparticles (1.7×10^{17}/mL) of iron oxide with a size of about 15 nanometres each, is introduced directly into the tumour or the wall of the cavity created after tumour resection. These nanoparticles are surrounded by a special coating, and attack the neoplastic tissue, sparing the adjacent healthy tissue. However, before they attack the neoplastic tissue, they are subjected to an alternating magnetic field, which is produced by a special generator — NanoActivator®. This magnetic field has a fast-changing effect, and the temperature of the nanoparticles increases, destroying neoplastic cells [27–29].

Effectiveness of magnetic nanoparticle heating and thermal modelling

The effectiveness of magnetic hyperthermia therapy (MHT) relies on delivering an appropriate thermal dose [30]. The minimum thermal dose delivered to any tumour region determines the overall treatment response [31, 32]. At low heating power, a localised distribution of magnetic nanoparticles (MNPs) results in a more pronounced anti-tumour effect compared to a more homogeneous MNP distribution [33]. Conversely, at high heating power, an inverse relationship between the MNP distribution and the anti-tumour effect occurs [27–29, 33].

Magnetic nanoparticle heating efficacy and thermal modelling

MHT effectiveness depends upon delivery of an appropriate thermal dose [30]. The lowest thermal dose that is delivered to any tumour region dictates the overall response to the treatment [31, 32]. At low heating power, localised MNP distribution produces a more pronounced anti-tumour effect compared to a more uniform MNP distribution [33]. The opposite relationship between MNP distribution and anti-tumour effect occurs at high heating power [27–29, 33].

Temozolomide as chemotherapy

Temozolomide (TMZ; DNA alkylating, nitrogen mustard derivative, dacarbazine, C6H6N6O2) was first introduced in 1999 (when it obtained the first license) for GBM, the most malignant grade [34]. TMZ (4-methyl-5-oxo-2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene-9-carboxamide) is a first-line chemotherapy drug approved for the treatment of GBM by the US Food and Drug Administration (FDA) [35] and the Occupational Safety and Health Administration (OSHA) [36]. Currently, the standard of care after surgical resection is radiotherapy (preferably IG-IMRT tomotherapy) with adjuvant TMZ [37], i.e. combination therapy followed by monotherapy. In combination therapy (tomotherapy and chemotherapy), TMZ is administered orally, usually at a dose of 75 mg/m^2 of body surface area per day for 42 days (up to 49 days), and targeted tomotherapy (60 Gy given in 30 doses). In the absence of complications, TMZ monotherapy is then administered after 4 weeks of combined therapy [37, 38].

It should be emphasised, however, that chemotherapy is toxic to proliferating cells, which is a beneficial effect, but by damaging healthy cells, it can cause many complications, e.g. thrombocytopaenia and neutropaenia, cytomegalovirus or hepatitis B virus, fatal liver failure, *Pneumocystis jirovecii*, or Stevens-Johnson syndrome [39–41].

Currently, medicine is being tested with temozolomide nano, or nanomedicine, as a new type of therapy. Nanocarriers play a role in glioblastoma treatment advance. Polymer nanoparticles have a polymer coating to protect the drug from early degradation. As a result, temozolomide nano is released continuously. The drug can also target the action of surface modification (attachment of specific ligands, peptides, antibodies, etc.) [42].

Pembrolizumab — humanised monoclonal antibody

In addition to TMZ, pembrolizumab has recently been used in the treatment of GBM (grade IV). The goal of this therapy is to restore the activity of T lymphocytes (using the patient's own immune system). Pembrolizumab blocks the PD-1 receptor (programmed cell death receptor) on the lymphocyte surface. In other words, this drug prevents the GBM from neutralising the lymphocytes by blocking the connection between the PD-L1 protein of GBM and the PD-1 receptor. This drug is administered to patients with diagnosed GBM

not only in the postoperative period but also before the planned surgical treatment of GBM [43–45].

A revolution in targeted (individual) therapy

The main current trends involve the study of mutations and tumour heterogeneity, which are essential in individual therapy. In patients with GBM, so-called cell-free DNA (cfDNA) was identified, which was extracted from plasma and fresh tumour samples. This study was conducted by Palande et al. [46] in a group of 180 patients in whom significantly elevated cfDNA was found compared to patients in the control group. In addition, these scientists detected "unique mutations" when studying cfDNA along with tumour DNA, which were consistent with the COSMIC database (the most often mutated genes were: *TP53*, 18.75%; *EGFR*, 37.5%; *NF1*, 12.5%; *LRP1B*, 25%; *IRS4*, 25%). Additionally, these scientists identified gene-to-gene fusions in cfDNA and tumour DNA as PDGFRA mutations. They also proved that PDGFRA fusion proteins play the main role in initiating therapy with protein kinase inhibitors (imatinib, sunitinib, and sorafenib). Interestingly, in their further studies, these researchers identified numerous genes (BCR-ABL1, COL1A1-PDGFB, and NIN-PDGFRB in 8% of patients and FGFR1-BCR in 4% of patients) in the patients' cfDNA, which could indicate the use of imatinib analogues. The use of other medications (such as crizotinib, entrectinib, or larotrectinib) is possible thanks to the ROS1 fusion (CEP85L-ROS1 and GOPC-ROS1), which has been demonstrated in the cfDNA of 8% of patients. These studies have additionally proven the amazing benefits of targeted therapy.

Tyrosine kinase inhibitors (imatinib, sunitinib, and sorafenib)

Protein kinases are enzymes that phosphorylate (phosphorylation is a chemical reaction involving the attachment of a phosphate group) other proteins in the cell, and thus regulate their activity. In normal cells, the activity of protein kinases is strictly regulated, while in cancer cells it is often out of control and excessive. This causes disturbances in the functioning of many cellular pathways and the control of the cell cycle, leading to the intensification of cell division and uncontrolled tumour growth. Inhibition of the excessive activity of protein kinases is the therapeutic goal of this group of anticancer drugs [46–50].

Imatinib

Imatinib is an organic chemical compound used as a drug in the form of a salt (metal sulfonate) in the treatment of many other cancers. Imatinib mesylate is metabolised mainly to the N-desmethyl derivative of piperazine with similar potency. The cytochrome P450 isoenzyme CYP3A4 participates in the biotransformation of imatinib. Imatinib competitively inhibits CYP2C9, CYP2D6, and CYP3A4/5 isozymes. This drug is the first inhibitor that inhibits tyrosine kinase receptors [47].

Sunitinib inhibits multiple receptor tyrosine kinases (RTKs) that are involved in tumour growth, neoangiogenesis, and metastatic disease dissemination. Sunitinib has been identified as an inhibitor of platelet growth factor receptors, vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptors (KIT), FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor 1 receptors (CSF-1R), and glial-derived neurotrophic factor receptors (RET). In biochemical and cell tests, the basic metabolite of sunitinib exhibits sunitinib-like activity [44, 48].

Sorafenib

Sorafenib is a multi-kinase inhibitor. This drug inhibits the Raf kinase and thus blocks the Raf signalling cascade. Additionally, cell division and proliferation are reduced. It also inhibits several tyrosine kinases, including those of the VEGF signalling pathway. Signalling cascades are blocked and tumour angiogenesis is reduced [49, 50].

Other medications

Other drugs include crizotinib, entrectinib, and larotrectinib. Recent studies by König et al. [51] indicate an exceptional treatment response of glioblastoma GMB to larotrectinib. This medication inhibits the tropomyosin kinase receptors TrkA, TrkB, and TrkC. This case allows for regular testing of NTRK fusion proteins.

Larotrectinib is the first drug specifically developed in its class and used in the treatment of any tumour harbouring certain mutations [51, 52]. Several earlier drugs, including pembrolizumab, were eventually approved by the FDA for treating specific mutations unique to cancer, but they were initially developed for certain cancer types [43, 44].

Individualised multimodal immunotherapy (IMI)

Effective immunotherapy can be achieved through 2 strategic approaches: anti-tumour vaccines and oncolytic viruses as a strategic approach. In the emerging field of immuno-oncology, anti-tumour vaccines and oncolytic viruses hold promise as treatment modalities. This type of immunotherapy, as an anti-tumour action, aims

to initiate a novel immune response or enhance existing immune responses against tumour cells [1].

Anti-tumour vaccines

Anti-tumour vaccines (CV) are used for active specific immunisation in patients with cancer. As a result, immunisation induces a reaction of T lymphocytes against the tumour. Among T lymphocytes, we can distinguish the following: 1. CD4+ T lymphocytes with Th1 polarization, 2. CD8+ cytotoxic T lymphocytes with T1 polarization (CTL), and 3. memory T cells reactive to tumour antigens (MTC) [1]. CVs activate specific immunisation, informing the patient's immune system about tumour-associated antigens (TA) [45]. Vaccines presenting tumour antigens (TA) can be based on peptides, DNA, and dendritic cells (DC) as antigen-presenting cells (APC) [1, 8]. It should be emphasised that, among others, dendritic cells (professional antigen-presenting cells) as anti-tumour vaccines can be loaded with specific peptides [53–56], autologous tumour lysate [8, 57], nucleotides (DNA [58] or RNA [59] obtained from the tumour, or viruses [60].

Oncolytic viruses

OVs, through selective replication, play a crucial role in destroying tumour cells, not only through direct viral oncolysis but also by inducing ICD. ICD leads to the recruitment of APCs, resulting in the promotion of APC maturation and interaction between APCs and dying cells. ICD promotes the phagocytosis of dying cells and enhances APC maturation. Additionally, ICD leads to the migration of APCs and facilitates cross-priming with T lymphocytes [1]. The German Centre for Immuno-Oncology (IOZK) in Cologne has developed IMI [8, 61]. Its aim is to stimulate strong specific immune responses mediated by T lymphocytes against tumour-associated antigens (TAA) in patients with tumours (with unique tumour neoantigens) [3]. These researchers have developed an anti-tumour vaccine named IO-VACR. This vaccine is individually produced for each patient. Besides dendritic cells (DCs), IO-VACR also contains avian OV or Newcastle disease virus (NDV), which enhances the vaccine's immunogenicity. The virus was first produced worldwide by IOZK in 2015 [61].

A new hope of radioactive iodine (^{131}I) therapy using NIS with or without the gene other than in glioblastoma multiforme

Attempts to use the anti-cancer effect of radioactive iodine by means of gene therapy using the sodium-iodine symporter include more and more cancers, even in organs where the NIS protein is not physiologically detected. This increases the scientific importance and, above all, the potential clinical use of the symporter in the future. Human cancer cell lines transfected with the NIS gene that have been successfully treated with radioactive iodine in animal models include the following: prostate cancer cells [62–64], multiple myeloma [65], non-small cell lung cancer, neuroendocrine tumours [66], malignant melanoma [63], adenocarcinoma of the breast and ovary [67], cervical cancer [68], renal cancer, GBM [62, 64], and primary liver cancer [69]. There is a dual advantage to performing NIS gene transfer: it is therapeutic and enables imaging of transgenic protein expression. The evaluation of transgenic protein expression requires an invasive biopsy or even the death of the animal subjected to gene therapy [70]. Meanwhile, the use of NIS gene transfer may enable non-invasive and reproducible visualisation of vector expression, which may be an important tool in preclinical and clinical gene therapy trials [71]. The use of the NIS gene as an imaging reporter gene (Imagene) allows the assessment of both the location and the concentration and duration of expression of the transgenic protein.

NIS, which is found in extrathyroid tissues, does not differ in primary structure — the cDNA of the NIS protein found in the parotid gland, mammary gland, and gastric mucosa has the same nucleotide sequence as the symporter gene found in the thyroid gland [72]. Gene therapy with the use of the NIS gene, however, requires the resolution of several issues, including whether post-translational processes, including the distribution of the NIS protein to the cell membrane, affect iodine uptake in cells expressing the exogenous symporter [71]. As many studies have shown, the cellular distribution of the symporter is a disorder-prone process and may, therefore, be a limiting factor for iodine uptake by the exogenous NIS protein. This highlights the role of ^{131}I therapy in a very significant way, and we must especially consider patients with hyperthyroidism. However, in our opinion, it is worth trying ^{131}I therapy even in patients with euthyroidism [73, 74], but what do we have to lose with a very heavy GBM therapy?

The use of radioactive iodine (^{131}I) in GBM therapy in animals

Over 60 years ago, Amyeset et al. [75] established the localisation of brain tumours (in rats) using radioactive iodine and phosphorus. More recently, in 2006 and 2007, positive effects of experimental treatment with ^{131}I therapy for glioma in animals (Wistar rats [69], and mice [67]) were reported (utilising a combination of the genetic *NIS* gene and ^{131}I therapy).

Of particular significance is the study conducted by Mamelak and Jacoby in 2007 [76]. This study involved a synthetic scorpion venom (from the giant yellow Israeli scorpion). The researchers, during phase I trials, identified TM-601 as a key component, which is a synthetic version of a peptide or protein molecule found in the venom of the aforementioned Israeli scorpion. TM-601, when binding to glioma cells, can penetrate the blood-brain barrier, allowing most substances, including radioactive iodine, to access brain tissue from the bloodstream. The researchers also determined that treating GBM with radioactive iodine and scorpion venom as a carrier, targeted specifically at glioma, did not produce adverse effects on neighbouring cells and organs. Clinical trials conducted on selected patient groups seem to confirm these findings.

Is it worth trying radioactive iodine (^{131}I) in humans?

One of the most significant advantages of radioimmunotherapy, as mentioned earlier, is the fact that administering ^{131}I therapy is completely safe. The only complication is thyroid dysfunction. Indeed, it has been recently demonstrated, for example in the case of thyroid cancer, that the maximum therapy dose is 37,000 MBq (1000 mCi). Considering the expression of the NIS gene in animals with GBM, the question arises whether it is worth using ^{131}I in GBM therapy but at doses ranging from 740 MBq (20 mCi) [77, 78] to as high as 5550 MBq (150 mCi) [77, 79].

Discussion

The main author of this article, A.Cz., possesses extensive expertise in ^{131}I therapy. As a nuclear physician, endocrinologist, and internist, she recently proposed a treatment approach for recurrent high-grade glioblastoma using radioactive iodine, commonly employed in thyroid disorders (toxic multinodular goitre, Graves' disease, toxic adenoma) [77] as well as malignant thyroid tumours [79]. In August 2021, A.Cz. was diagnosed with GBM, and the glioma (stage IV) was surgically removed shortly after diagnosis. Subsequently, she underwent radio- and chemotherapeutic treatment. Following that, she initiated concurrent chemoradiotherapy with temozolomide (TMZ; 75 mg/m^2/day) and external beam radiotherapy (60 Gy in 30 fractions), which was well-tolerated. Chemotherapy was continued (5 days per week for a month at the Greater Poland Cancer Centre in Poznan). From November 2021 to April 2023, she started additional immunotherapeutic (virological) treatment and received 2 doses of GBM anticancer vaccine at the IOZK (Immun-Onkologisches Zentrum Köln). During immunotherapy at IOZK, Keytruda (pembrolizumab) was administered. In December 2022, thanks to the efforts of oncologists at WCPIT (Greater Poland Centre of Pulmonology and Thoracic Surgery, Oncology Department), the Keytruda treatment became accessible to A.Cz. under the National Health Fund.

Following a follow-up MRI examination on 4 March 2023, when A.Cz. felt unwell, it was revealed that there was a relapse (3T MRI Siemens Magnetom Skyra axial images). In the postoperative and postradiotherapy lesions of the left temporal lobe, hyperintensity was observed in the T2 sequence (Fig. 1A). Moreover, there was a substantial enhancement in the T1 sequence after contrast administration, raising suspicion of recurrence (Fig. 1BC). Urgent consultation indicated the necessity for immediate chemotherapeutic and immunotherapeutic treatment. While awaiting therapy, with little to lose, A.Cz. received an ablative dose of 2960 MBq (80 mCi) of ^{131}I. Three days before radioactive ^{131} therapy, she prophylactically blocked iodine uptake by the thyroid (Kelp 300 mg). ^{131}I therapy was administered as quickly as possible (self-administered) because she was feeling very unwell (experiencing severe headaches, visual disturbances, and gait impairment). Approximately 24 hours after ^{131}I therapy, she began to feel significantly better. On 12 June 2023, 3T MRI Siemens Magnetom Skyra axial images showed regression in the hyperintense lesions of the left temporal lobe in the T2 sequence (Fig. 2A). Significant regression was also observed in the T1+C sequences (Fig. 2BC). These findings clearly indicate a 30% reduction in GBM following radioactive iodine ^{131}I administration (in addition to standard therapy).

Currently, neurosurgical treatment remains the standard in GBM management, combined with adjuvant therapy in the form of radiotherapy and chemotherapy. Neurosurgical surgery, especially with the use of 5-ALA, enhances the effectiveness of surgical interventions by enabling the differentiation of healthy tissues from remaining small tumour fragments that are indistinguishable from healthy tissues under normal daylight. The extent of resection is therefore more comprehensive. Simultaneously, although a larger area of pathological changes is removed through the operation, this method poses less risk to the patient [15–17].

After tumour removal, tomotherapy is applied instead of conventional radiotherapy, which contributes to better protection of healthy tissues. In parallel, adjuvant temozolomide is used. The application of nano-sized temozolomide, i.e. nanomedicine, is being tested as a new type of therapy. Unfortunately, there are situations where, due to the infiltrative growth

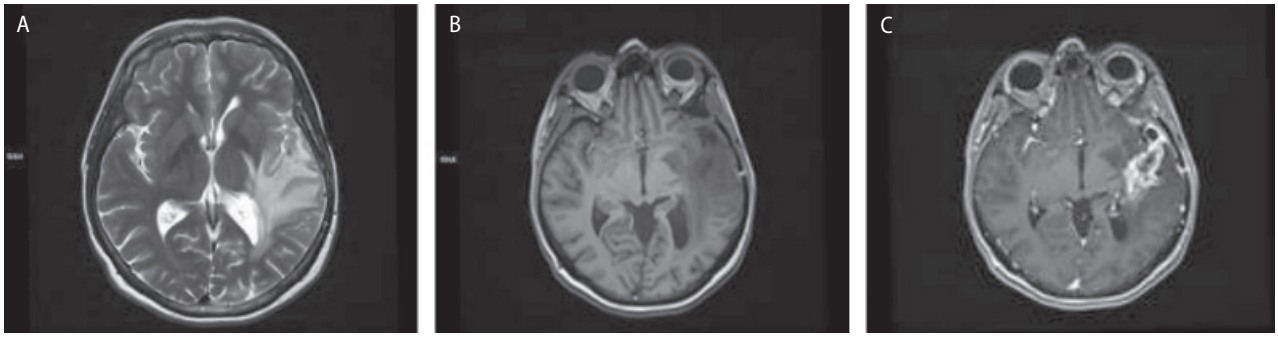

Figure 1. *(3 April 2023) 3T MRI Siemens Magnetom Skyra axial images.* **A.** *In left temporal lobe postoperational and postradiotherapy lesions, hyperintense on T2 sequence;* **BC.** *Strong enhancement on T1 sequence after contrast administration suspected of recurrence*

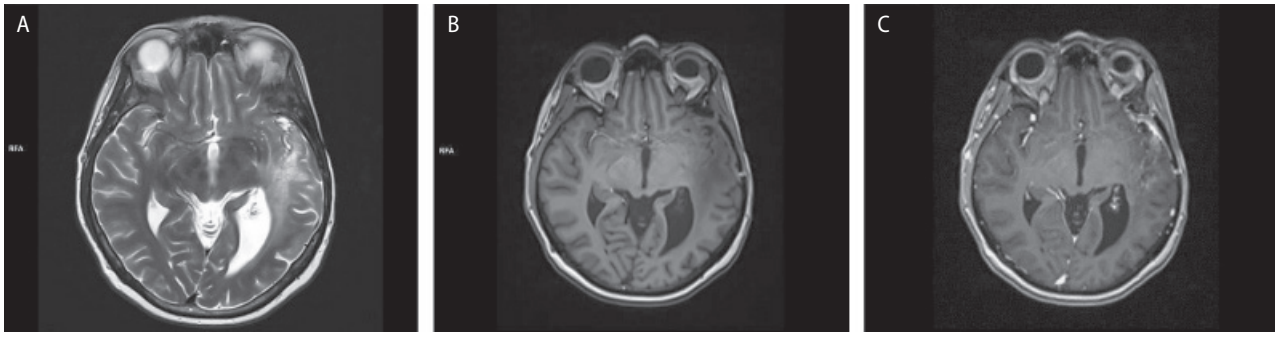

Figure 2. *(12 June 2023) 3T MRI Siemens Magnetom Skyra axial images.* **A.** *In left temporal lobe postoperative and post-radiotherapy lesions, hyperintense on T2 sequence with relevant regression;* **BC.** *Important regression has also been on T1+C sequences*

nature of the tumour and its location, surgery cannot be performed on the tumour. Therefore, the focus is on IMI. It is based on the individuality of immunological tumour-host interactions and the concept of ICD induced by oncolytic virus [1]. The same author, in another publication, demonstrated that PAMP, DAMP, and endoplasmic reticulum (ER) play a crucial role in OV-induced ICD. As previously mentioned, attenuated avian RNA virus or oncolytic NDV can serve as examples of OV, which is an essential life-saving virus [80].

OVs refer to non-pathogenic viruses that selectively infect cancer cells and cause oncolysis, thereby initiating post-oncolytic antitumour immunity. Similarly to other agents (e.g. certain chemotherapeutics, ionizing radiation), OVs can be classified as inducers of ICD [81]. Oncolytic viruses are viruses that have the ability to replicate in cancer cells while lysing them or breaking them down. Galluzzi et al. [82] demonstrated that ICD induces immunogenic apoptosis, necroptosis, pyroptosis, and autophagic (oncotic) cell death. In summary, ICD facilitates the recruitment of APCs, directs the interaction between APCs and dying cells, promotes the phagocytosis of dying cells, enhances APC maturation, migration, and cross-priming with T lymphocytes.

Treatment with OVs has proven to be significantly beneficial and safe, with few side effects. However, there are instances where OVs encounter challenges in infecting cancer cells because before the OV reaches an infected cell, it encounters natural mechanisms that prevent its dissemination throughout the body. Nevertheless, it has been demonstrated that oncolytic NDV can overcome treatment resistance [58, 80].

This is how the immune system works — upon recognising the virus, it defends itself and attempts to destroy the intruder. This means that OVs must reach an infected cell before being recognised and destroyed by the immune system. Despite these difficulties, researchers continue to study other types of cancer, including melanoma, pancreatic cancer, and breast cancer. Perhaps, in GBM therapy, it is worth trying something entirely new.

Should we consider introducing the *NIS* gene into extrathyroidal tumours? Kitzberger et al. [83] have introduced a significant and forward-looking non-virological gene therapy approach for extrathyroidal tumours in clinical translation of *NIS* gene therapy. This therapy represents an effective and safe development of gene delivery carriers that allow for sufficient and selective NIS tumour expression levels. Kitzberger et al. further

demonstrated that this occurs when the vector is applied systemically. Besides monitoring and targeting primary tumours, some of these approaches provide options for treating metastases through improved targeted delivery of the *NIS* transgene. Non-viral vector systems for targeted *NIS* gene transfer to tumours other than the thyroid are currently being investigated by our group in cooperation with E. Wagner and P. Nelson from Ludwig-Maximilians-University Munich and are summarised in this review. Synthetic polyplexes and mesenchymal stem cells can deliver antitumour therapy through various targeting strategies after systemic administration. Both systems are promising platforms with potential for clinical success [83]. As previously shown, NIS is also present in other organs [72, 84–92].

The sodium-iodide symporter found in extrathyroidal tissues does not differ in primary structure — cDNA from the NIS protein present in the parotid gland, breast gland, and gastric mucosa has the same nucleotide sequence as the symporter gene located in the thyroid [72]. In extrathyroidal tissues, NIS protein expression is regulated differently and is generally weaker than in the thyroid [83]. Therefore, it raises the question of whether it is worthwhile to treat these other tumours (not just thyroid) with ^{131}I therapy alone but at significantly increased doses. And what is the risk, considering that GBM patients have a very short lifespan, and this could be a "revolution"? The only "complication" is thyroid dysfunction. So, perhaps it is worth trying, especially when the patient has nothing to lose.

Based on these results, one can speculate that ^{131}I therapy may be an alternative for patients with recurrent glioblastoma multiforme. However, such a hypothesis requires further confirmation and verification through broader clinical trials. But what is the risk of administering ^{131}I therapy as quickly as possible (during standard therapy)? In the case of GBM patients, time is of the essence, as previously mentioned, because they have very short life expectancies.

I did this under the influence of publications reporting positive outcomes of experimental glioma treatment with ^{131}I therapy, both in animals (Wistar rats [69] and mice [67] — combining NIS genetics and ^{131}I therapy), and interestingly, over 60 years ago, Amyes et al. [75] determined the location of brain tumours (in rats) using radioactive iodine and phosphorus.

Conclusion

The standard treatment, immunotherapy, and the administration of ^{131}I therapy are presented as something completely new in therapy. The question of whether the use of ^{131}I therapy is fully satisfactory in breast cancer, lung cancer, or glioblastoma multiforme treatment remains unanswered. Although our observations are significant as a clinical study, we have not addressed NIS expression, and there is still no clear evidence of the effect of ^{131}I therapy alone in recurrent glioblastoma. But perhaps it is worth taking the risk, because the most important thing is that life is worth living, and can ^{131}I therapy help with that, or contribute to healing. We have more time for the effect, but something incredible has been shown preliminarily. Just like in thyroid cancer, sometimes ^{131}I therapy may need to be repeated to see the effect again. Therefore, in our publication, it has been demonstrated that the administration of ^{131}I therapy significantly reduces GBM by 30%. This is something unbelievable.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

Conceptualisation, A.Cz., P.G. and J.S.; Methodology, A.Cz. P.G. and J.S.; Software, A.Cz., P.G. and J.S.; Validation, A.Cz., P.G. and J.S.; Formal Analysis, A.Cz., P.G., J.S., K.D., N.S.G., K.K., P.S., M.W., J.M., J.K., K.P., P.G., M.R.K., E.F., E.Sz-P., M.R., A.F.; Investigation, A.Cz., P.G., J.S., K.D., N.S.G., K.K., P.S., M.W., J.M., J.K., K.P., M.R.K., E.F., E.Sz-P., M.R., A.F.; Resources, A.Cz.; Data Curation, A.Cz.; Writing – Original Draft Preparation, A.Cz., P.G., J.S., K.D., N.S.G., K.K., P.S., M.W., J.M., J.K., K.P., P.G., M.R.K., E.F., E.Sz-P., M.R., A.F.; Writing – Review & Editing, A.Cz., P.G., J.S., K.D., N.S.G., K.K., P.S., M.W., J.M., J.K., K.P., P.G., M.R.K., E.F., E.Sz-P., M.R., A.F.; Visualization, A.Cz., K.D.; Supervision, A.Cz.; Project Administration, A.Cz.; Funding Acquisition, A.Cz.

A.Cz., gave herself radioactive iodine (^{131}I) therapy as a Doctor of nuclear medicine. J.M., J.K. performed neurosurgery and K.K., P.S., and M.W. performed MRI. A.Cz. is waiting for histopathological results from Bydgoszcz (University). All authors read and approved the final manuscript.

Informed consent statement

Informed consent was obtained from A.Cz. involved in the study.

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