Pielęgniarstwo w opiece długoterminowej
Kwartalnik międzynarodowy

LONG-TERM CARE NURSING
INTERNATIONAL QUARTERLY

ISSN 2450-8624 e-ISSN 2544-2538
tom 8, rok 2023, numer 3, s. 8-17 vol. 8, year 2023, issue 3, p. 8-17
DOI: 10.19251/pwod/2023.3(2)

Aleksandra Orzechowska[1,A,D], Julia Orzechowska[2,D], Karolina Ziętara[1,B], Mateusz Pawlina[1,E], Natalia Pawełczak[1,B], Aleksander Oskroba[1,C], Cezary Stawikowski[3,E], Karolina Raksa[1,D], Ilona Kowalczyk[4,C], Bartłomiej Zielonka[3,E], Piotr Pawłowski[1,F]

GLIOBLASTOMA MULTIFORME - THE LATEST TREATMENT OPTIONS

Glejak wielopostaciowy - najnowsze możliwości leczenia

[1] Faculty of Medicine, Medical University of Lublin, Polska
[2] Faculty of Dentistry, Medical University od Lublin, Polska
[3] Resident, 1st Military Clinical Hospital in Lublin, Polska
[4] Resident, Independent Public Clinical Hospital prof. W. Orlowski CMKP in Warsaw, Polska

A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

Aleksandra Orzechowska - 0000-0002-6919-0928
Julia Orzechowska - 0000-0001-6516-9331
Karolina Ziętara - 0000-0002-6754-9263
Mateusz Pawlina - 0000-0001-7354-4883
Natalia Pawełczak - 0000-0001-9933-258X
Aleksander Oskroba - 0000-0003-0783-4895
Cezary Stawikowski - 0000-0003-3026-8617
Karolina Raksa - 0000-0001-5571-1035
Ilona Kowalczyk - 0000-0002-8669-3068
Bartłomiej Zielonka - 0000-0001-7788-1342
Piotr Pawłowski - 0000-0002-1197-7218

Abstract (in Polish):
Wstęp: Glejak wielopostaciowy jest chorobą nowotworową ośrodkowego układu nerwowego. Charakteryzuje się on szybką angiogenezą, wysokim indeksem proliferacji, znaczną heterogennością komórek oraz stosunkowo późną możliwością rozpoznania. Leczenie glejaka wielopostaciowego opiera się przede wszystkim na chemioterapii, radioterapii i chirurgicznej resekcji guza. W związku z wysokim zaawansowaniem choroby w momencie diagnozy, remisja jest praktycznie niemożliwa.
Cel pracy: Celem pracy jest wskazanie najnowszych możliwości leczenia glejaka wielopostaciowego.
Materiał i metody: Dokonano przeglądu anglojęzycznego piśmiennictwa naukowego z lat 2012 – 2022, pochodzącego z baz danych takich jak PubMed, SCOPUS, Web of Science, Google Scholar. Wyszukiwania przeprowadzono według słów kluczowych: glejak wielopostaciowy, GBM, chemioterapia, immunoterapia. Do analizy zakwalifikowano 25 pozycji literaturowych.
Wyniki i wnioski:
- Pomimo postępu nauki, glejak wielopostaciowy nadal nie jest chorobą uleczalną.
- Duże nadzieje pokładane są w nośnikach molekularnych, które mogą przekroczyć barierę krew-mózg i dotrzeć bezpośrednio do guza.
- Immunoterapia staje się znacznie lepszą alternatywą dla niespecyficznej chemioterapii.
- Obiecujące mogą być dalsze badania nad zastosowaniem terapii CAR-T w leczeniu guzów litych.
- Istotną rolę w opiece nad pacjentem z GBM pełni personel pielęgniarski.

Abstract (in English):
Background: Primary brain tumors account for up to 2% of all malignancies. Of these, glioblastoma multiforme (GBM) is the most common. GBM is one of the primary tumors of the central nervous system with a very high degree of malignancy – IV according to the classification of the WHO. The survival time from diagnosis in most patients is only a dozen or so months, and the median survival is about 12 months. Only 3–8% of patients live longer than 3 years.
Aim of the study: The aim of the study is to indicate the latest treatment options for glioblastoma multiforme.
Material and methods: English-language scientific literature from 2012 - 2022 from databases such as PubMed, SCOPUS, Web of Science, Google Scholar was reviewed. Searches were conducted according to keywords: GBM, glioblastoma multiforme, immunotherapy, chemotherapy. 25 items of literature were qualified for analysis.
Results and conclusions: Despite advances in science, glioblastoma is still not a curable disease. Large amounts are placed in molecular carriers that can cross the blood-brain barrier and reach the tumor directly. Immunotherapy is becoming an effective alternative to non-specific chemotherapy, which is also associated with fewer systemic side effects. The results of studies on the use of CAR-T therapy in the treatment of solid tumors are becoming more and more promising. What is more, nursing staff play an important role in the care of a patient with GBM.

Keywords (in Polish): glejak wielopostaciowy, GBM, chemioterapia, immunoterapia.

Keywords (in English): GBM, glioblastoma multiforme, immunotherapy, chemotherapy.

Received: 2023-08-05
Revised:
Accepted: 2023-09-18
Final review: 2023-09-14

Short title
GBM - treatment

Corresponding author
Aleksandra Orzechowska
Faculty of Medicine, Medical University of Lublin, Polska;
email: olaorzechowska14@gmail.com

Authors (short)
A. Orzechowska et al.

Introduction

Primary brain tumors account for up to 2% of all malignancies. Of these, glioblastoma multiforme (GBM) is the most common. The probability of incidence increases with age and reaches 50/100,000 at the age of 75. Nearly half of all CNS cancers in adults are high-grade tumors. of them the most common, accounting for up to 60% of these tumors, and in people over 60, up to 80% have glioblastoma multiforme. GBM is one of the primary tumors of the central nervous system with a very high degree of malignancy. The survival time from diagnosis in most patients is only a dozen or so months, and the median survival is about 12 months. Only 3–8% of patients live longer than 3 years. It is assigned the highest, IV degree of malignancy according to the classification of the World Health Organization (WHO, World Health Organization) [1,2].

The symptoms of glioblastoma multiforme are diverse and are related to the location of the tumor. May occur:

- headaches
- neurological deficits;
- qualitative disorders of consciousness, emotional, cognitive and personality
- seizures
- quantitative disorders of consciousness (as a sign of advanced cancer);

Presence of significant neurological deficits and psycho-organic syndrome is considered a poor prognostic factor for malignant gliomas of the brain. Epilepsy, in turn, is associated with a better prognosis for brain gliomas, although it is not independent prognostic factor. This symptom more often accompanies tumors of a smaller size biological aggressiveness, such as oligodendroglioma [3].

On computed tomography (CT), the GBM is an irregular hypotensive mass with a central zone of low density, corresponding to necrosis. Hemorrhagic foci in GBM are described in almost 19% of cases, while calcifications are very rare and probably related to malignant conversion of a previous less malignant glioma. A distinctive feature of GBM is the extensive zone edema, usually significantly increasing weight. After administration contrast agent is found to be strong, heterogeneous strengthening within the wide, irregular peripheral part of the tumor. In MR it is characterized by a heterogeneous signal associated with the presence of retrograde lesions. It undergoes a strong, irregular, marginal contrast enhancement, then the border between the necrosis and the solid part of the tumor is visible. Although the vast majority of these tumors are unifocal, multicentric tumors have been described. Especially in MRI, in T2-weighted images irregular, banded zones of edema located outside the main lesion indicate the penetration of the tumor into an area of apparently unchanged tissue [4, 5].

Current standard medical treatment of malignant gliomas includes surgical resection followed by external beam radiation and chemotherapy. Despite that complex approach, the outcome of that treatment is still not satisfactory. Radiotherapy is the main method of treating patients with malignant tumors brain gliomas undergoing diagnostic or cytoreductive treatment neurosurgery. The standard procedure after surgery is irradiation up to a dose of 60.0 Gy in fractions of 2.0 Gy (6 weeks of treatment) in young patients and in good general and neurological condition. Patients in advanced age, in poor general or neurological condition are not eligible for radiotherapy. Chemotherapy plays an undisputed role in the treatment of recurrences of highly differentiated gliomas. It allows for long-term stabilization of tumor growth and often also clinical improvement. Over the last 2 decades, nitrosourea compounds, especially carmustine (BCNU), have been widely believed to be the most active drugs in chemotherapy regimens for patients with malignant brain gliomas [6, 7, 8].

Almost all secondary GBMs have mutations in the IDH1 gene, while primary GBMs are very rare. Primary GBMs are very heterogeneous gliomas and are characterized by a variety of genetic changes. One of them is the expression of a mutated form of the EGFR gene. The most common mutation is EGFR-vIII activating the abnormal receptor. Thanks to this molecular knowledge, it is possible to better tailor therapy for the patient. Current treatment options for patients with glioblastoma multiforme (GBM) are insufficient because there are many problems such as tumor heterogeneity, blood-brain barrier and glioblastoma stem cells. One of the possible solutions are combination therapies, which can be additionally enriched with the use of nanocarriers to increase the effect of drugs. It is also possible to use brachytherapy, the introduction of radioisotopes or the use of steroids [9, 10, 11].

Aim of the study

The aim of the study is to indicate the latest treatment options for glioblastoma multiforme.

Material and methods

Information on the methodology of the study is shown in Figure 1.
There was used a non-systematic review of English-language literature.

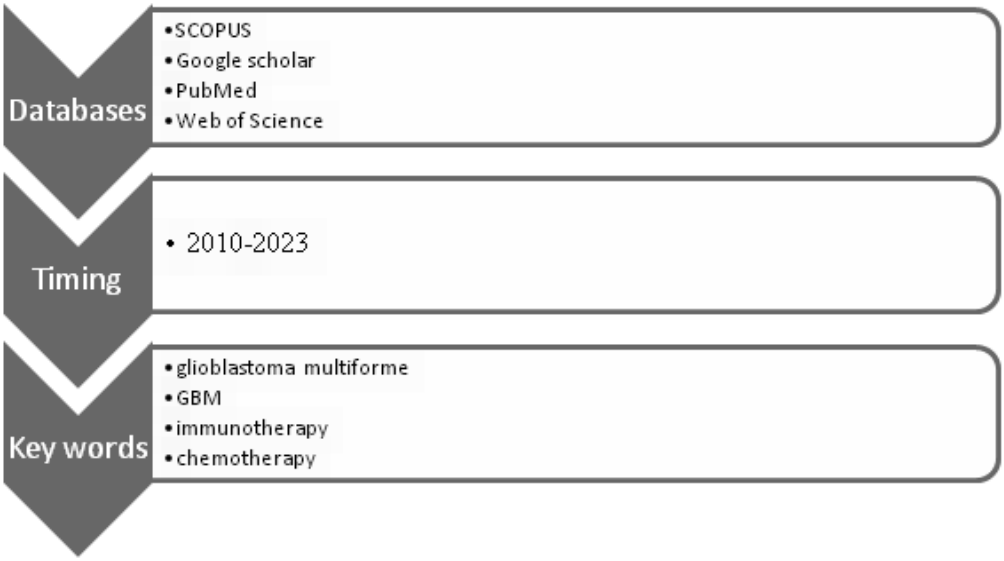

Figure 1.Schematic of the study methodology.

Results

Overcoming the blood-brain barrier

In many cases, the blood-brain barrier is a very useful filter for unfavorable pathogenic microorganisms or drugs that are toxic to the central nervous system. In the presence of glioblastoma multiforme, however, it is an obstacle that significantly hinders access to the tumor for drugs that can potentially render it harmless. The main problems of drug delivery to brain tumors are related to overcoming the blood-brain barrier and ensuring the selective transport of drugs to tumor cells. Selective transport requires properly designed drug delivery systems. Multiple emulsions, next to polymerosomes, nanoparticles or microemulsions, are considered as drug carriers that can solve the problems of treating brain tumors. One way to bypass the blood-brain barrier is to deliver drugs intraoperatively, e.g. by introducing implants with drugs [12], [13].

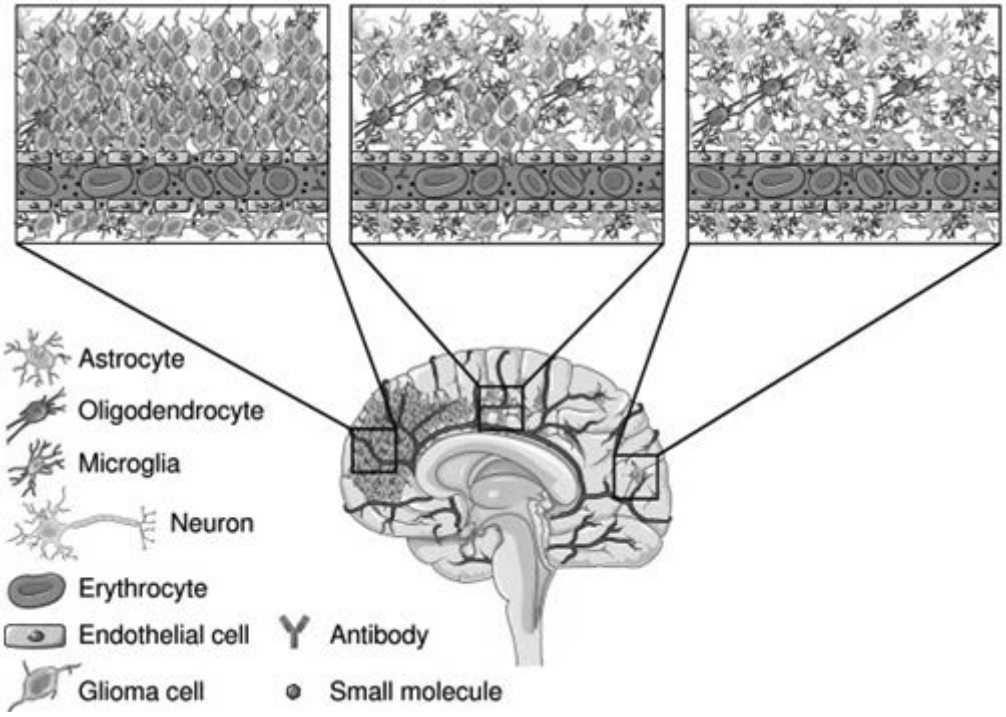

Figure 2. Different regions of glioblastoma multiforme characterized by the varying degree of BBTB integrity.

GBM therapeutics need to be able to cross this barrier and penetrate the brain to reach the tumor. Standard of care involves maximal surgical resection, followed by radiotherapy and concurrent chemotherapy with temozolomide (TMZ). TMZ is an orally administered alkylating agent that can be transported across the BBB and has remarkable distribution at the tumor site [14].

The blood-brain barrier is impermeable to siRNAs with an average molecular weight of around 14 kDa (about 40 nucleotides). The strategy of increasing the permeability of the blood-brain barrier with the use of osmotic agents, e.g. mannitol, is used. There are also attempts to break this barrier using pharmacological methods using the bradykinin analog RMP-7. In vivo, in the rat, PILs (pegylated immunoliposomes) with a diameter of 85 nm, combined with a monoclonal antibody for the rat transferrin receptor (TfR), effectively passed through the blood-brain barrier and the tumor membrane. Inside, they contained a vector from which shRNA (short hairpin RNA) was expressed, silencing the luciferase reporter gene. Another possibility is the use of coated

nanoparticles resembling low-density lipoproteins (LDL), which can interact with endothelial LDL receptors and cross the barrier [15].

Immunotherapy

Glioblastomas are effective at escaping host immune surveillance. Indeed, one of the hallmarks of cancer is the ability to evade cellular immunity. Immunotherapies seek to re-direct immune cells against a tumor by exploiting a patient's immune system. Tumor progression is dependent on angiogenesis, and anti-VEGF therapy has been shown to be effective in many oncological diseases. Bevacizumab is a humanized monoclonal antibody that binds to VEGF and inhibits its activity. Combination of bevacizumab with irinotecan (a cytostatic agent acting by inhibiting topoisomerase I) may be an active therapeutic option in recurrent WHO grade III and IV brain gliomas. By binding to vascular endothelial growth factor A (VEGF-A) and preventing its interaction with VEGF receptor tyrosine kinases VEGFR1 and VEGFR2 on the surface of endothelial cells, bevacizumab inhibits the growth of human tumor cell lines including GBM. An unequivocal effect of anti–VEGF-A activity exerted by bevacizumab is its antivascular properties, including vascular normalization and reduction of vascular permeability, which induces an antiedema effect. What is more, additional features included reduction in microvascular proliferation and microvessel density, consistent with those seen in mice orthotopic models [16, 17, 18].

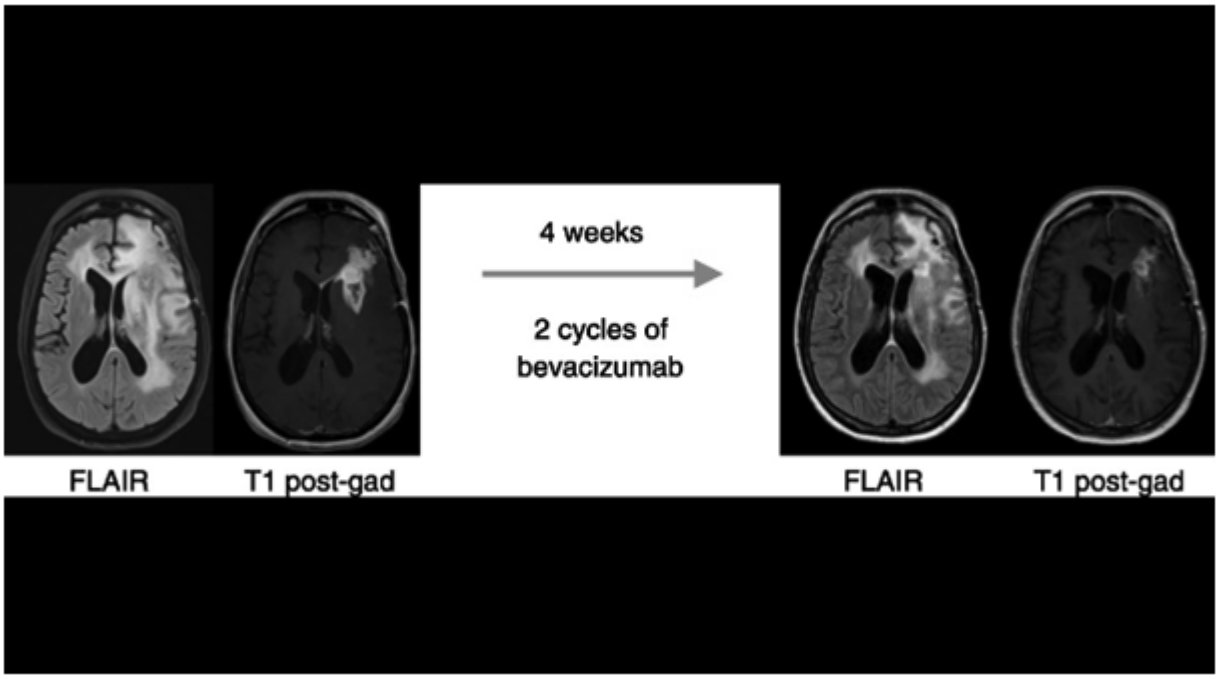

Figure 3. Characteristic improvement of FLAIR and T1 postgadolinium enhancement in a patient with recurrent GBM following 2 cycles of bevacizumab treatment.

EGFR expression

The epidermal growth factor receptor (EGFR) belongs to the group of tyrosine kinase receptors, i.e. the ErbB family. The receptor consists of three regions: an extracellular ligand-binding region, an intracellular region and a transmembrane domain which anchors the molecule in the cell membrane. EGFR overexpression is present on the surface of the neoplastic cells of many cancer types and it is a negative prognostic factor. EGFR overexpression in 10 to even 50% of GBM cases. Binding of the

ligand to the EGFR receptor leads to activation of the intracellular transmission cascade. Linkage of the ligand to the extracellular domain EGF receptor is "trigger mechanism", the effect of which is to initiate a sequence of intracellular events. Currently, preparations interfering with EGFR activity are used in clinical practice. Increasingly, EGFR-targeted treatment is combined with other anti-cancer treatments, giving cancer patients a chance to prolong their lives [19, 20, 21].

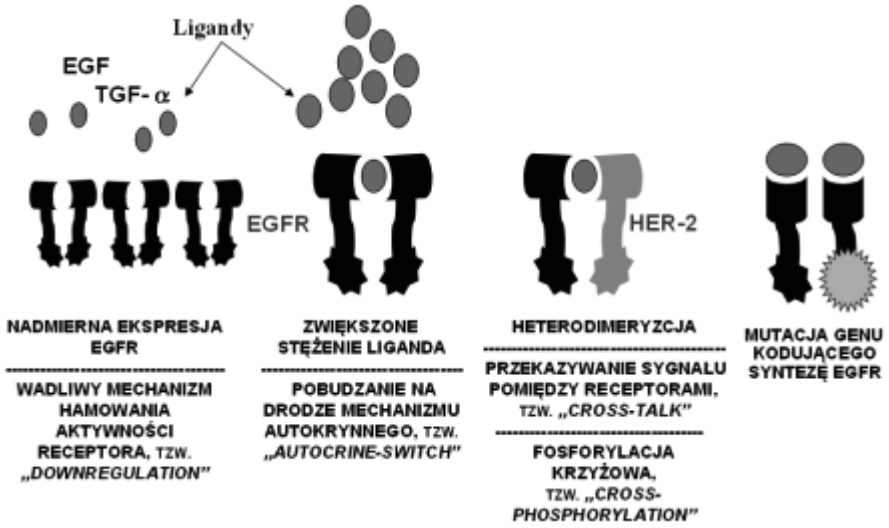

Figure 4. Mechanisms of excessive EGFR activity; EGF (epidermal growth factor) - epidermal growth factor; EGFR (epidermal growth factor receptor) – epidermal growth factor receptor; HER-2 (ErbB-2) – a receptor from the ErbB family; TGF-α (transforming growth factor - α) - transforming growth factor – α.

CAR-T

CAR-T (chimeric antigen receptors T cell therapy) is an immunotherapy belonging to the ATMP (advanced therapy medicinal products). CAR-T technology, in which the letter C comes from the word chimera, is a combination of two types of specific response of the immune system - cytotoxic (T lymphocytes) and humoral (antibodies). This therapy is based on the cancer patient's own T lymphocytes. T cells stay genetically modified to recognize and eliminate cancer cells from the body. In addition removal of tumor cells occurs without prior presentation of antigens to T cells via major histocompatibility proteins (major histocompatibility complex - MHC). CAR-T therapy is increasingly used in the treatment of solid tumors. The mutated epidermal growth factor receptor (EGFRvIII), which is present in 20-30% of glioblastoma cells, may be an ideal target. In contrast to haematological malignancies, in solid tumors both T cell trafficking and infiltration are often strongly constrained by the tumor microenvironment. It seems that a good way to overcome the tumor microenvironment that suppresses the host's immune response would be to create interleukin-12-producing CAR-T cells. IL-12 induces host immune mechanisms of action [22, 23, 24].

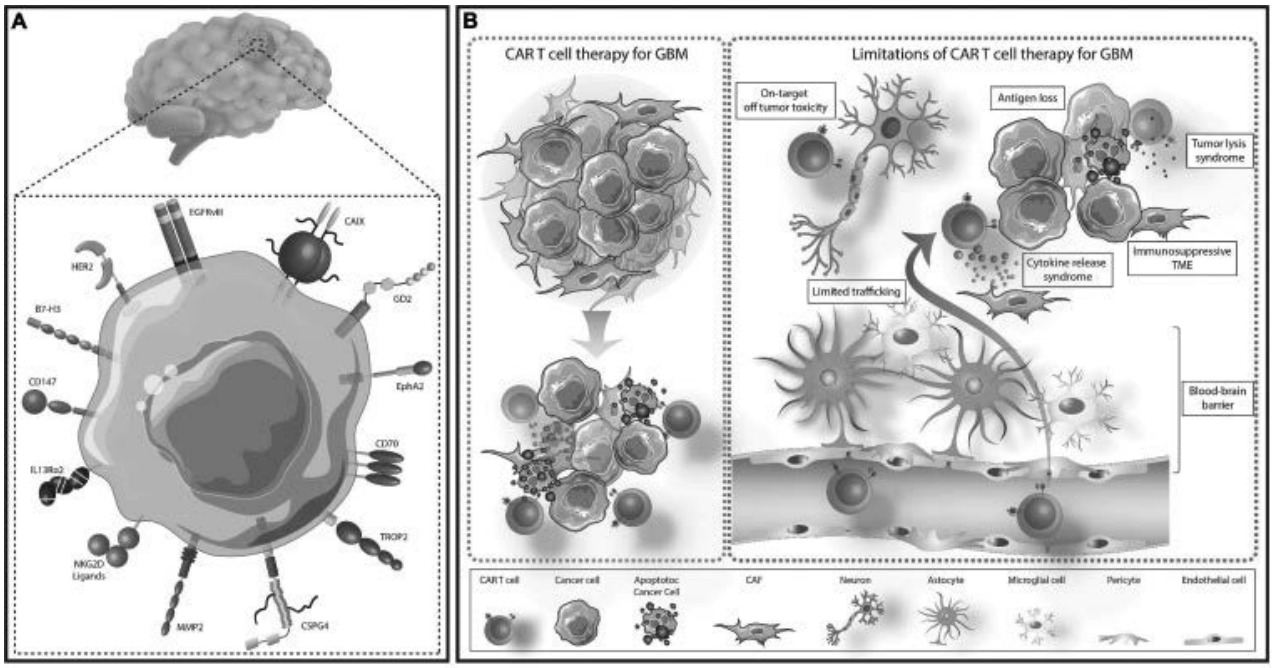

Figure 5. Summary of CAR T cell treatment for GBM. GBM cells express several targetable TAs which have either been assessed in clinical or preclinical CAR T cell studies (A). TA-specific CAR T cells can be administered to patients to recognize and eliminate TA expressing GBM cells (B). However, several limitations hinder this process. These include; the immunosuppressive TME, limited access across the BBB, on-target, off-tumor toxicity, cytokine release syndrome, tumor lysis syndrome, and selective antigen loss.

Nursing role

Patients suffering from primary neurological tumors often require round-the-clock care that cannot be provided by medical doctors - only by nursing staff. This is related to the complexity of the needs patients and their carers in a very short period of time survival, presence of progressive neurological symptoms, sometimes relatively young age of patients. The most important in this case is nursing care, which provides anti-edematous treatment, antithrombotic prophylaxis or anti-decubitus measures [25].

Conclusions

- Despite advances in science, glioblastoma is still not a curable disease.
- High hopes are placed on molecular carriers that can cross the blood-brain barrier and reach the tumor directly.
- Immunotherapy is becoming a much better alternative to non-specific chemotherapy.
- Further research on the use of CAR-T therapy in the treatment of solid tumors may be promising.
- Nursing staff play an important role in the care of a patient with GBM.

Additional materials

- Figure 1.- Schematic of the study methodology (source: own elaboration).
- Figure 2.- Different regions of glioblastoma multiforme characterized by the varying degree of BBTB integrity (source:https://www.sciencedirect.com/science/article/pii/S1368764615000126?via%3Dihub#fig0005*)*
- Figure 3.- Characteristic improvement of FLAIR and T1 postgadolinium enhancement in a patient with recurrent GBM following 2 cycles of bevacizumab treatment. (source: Bevacizumab and Glioblastoma: Past, Present, and Future Directions; The Cancer Journal24(4):180-186, July/August 2018.)
- Figure 4.- Mechanisms of excessive EGFR activity (source: Wojtukiewicz M. Z. Podstawy biologiczne terapii ukierunkowanej na receptor czynnika wzrostu naskórka (EGFR), Journal of Oncology, 2008, vol. 58)
- Figure 5.- Summary of CAR T cell treatment for GBM. (source: Maggs L. at al. CAR T Cell-Based Immunotherapy for the Treatment of Glioblastoma; Front Neurosci 2021.)

Referents

1. Rojek A., Zub W. L., Waliszewska-Prosół M., Bladowska J., Obara K., Ejma M., Wieloletnie przeżycie chorych z glejakiem wielopostaciowym — opisy przypadków, Pol. Przegl. Neurol 2016;12(2):107-115.
2. Bigos Ewelina, Spych Michał, Masłowski Michał, Gottwald Leszek, Fijuth Jacek: Glejak wielopostaciowy mózgu - problem coraz bardziej aktualny, Medycyna Paliatywna, vol. 6, no. 1, 2014, pp. 7-13.
3. Kępka L., Aktualne zasady postępowania diagnostyczno-terapeutycznego w onkologii, rozdz. Nowotwory ośrodkowego układu nerwowego , pod red. dr. n. med. Janusza Medera, 2011.
4. Ejma M., Waliszewska-Prosół M., Hofman A., Bladowska J., Zub L. W., Podemski R., Rzadkie kliniczne odmiany glejaka wielopostaciowego, Postepy Hig Med Dosw (online), 2014; 68: 316-324.
5. Walecki J., Chojnacka E., Diagnostyka obrazowa guzów wewnątrzczaszkowych. Część I — guzy neuroepitelialne, Onkologia w Praktyce Klinicznej Tom 3, nr 4, 2007, 177–197.
6. Turek G., Pasterski T., Bankiewicz K., Dzierzęcki S., Ząbek M., Current strategies for the treatment of malignant gliomas – experience of the Department of Neurosurgery, Brodno Masovian Hospital in Warsaw, 2020.
7. Spych M., Klonowicz M., Łuniewska-Bury J., Fijuth J., Rola radio- i chemioterapii u chorych na złośliwe glejaki mózgu, Polski Przegląd Neurologiczny Tom 3, Nr 3, 2007.
8. Nawrocki S., Cieślak E., Postępy w leczeniu nawrotów złośliwych glejaków mózgu, Współczesna Onkologia (2006) vol. 10; 7 (334–339).
9. Potemski P., Molekularne uwarunkowania leczenia glejaków, Onkologia w Praktyce Klinicznej 2010, tom 6, nr 2, 73–78.
10. Dębska S., Owecka A., Czernek U., Szydłowska-Pazera K., Habib M., Potemski P., Transportery błonowe ABCC – budowa, funkcja i znaczenie w mechanizmach wytwarzania oporności

wielolekowej w komórkach nowotworów złośliwych, Postepy Hig Med Dosw (online), 2011; 65: 552-561.
11. Bigos E., Spych M. K., Masłowski M., Gottwald L. M., Fijuth J., Glejak wielopostaciowy mózgu – problem coraz bardziej aktualny, Medycyna Paliatywna 2014; 6(1): 7–13.
12. Van Tellingen O., Yetkin-Arik B., de Gooijer M. C., Wesseling P., Wurdinger T., de Vries H. E., Overcoming the blood–brain tumor barrier for effective glioblastoma treatment, Drug Resistance Updates, Volume 19, March 2015, Pages 1-12.
13. Dłuska E., Markowska-Radomska A., Metera A., Emulsyjne platformy do podawania leków, Baza Wiedzy Politechniki Warszawskiej, 2018.
14. Zhao M., van Straten D., L D Broekman M., Préat V., M Schiffelers R., Nanocarrier-based drug combination therapy for glioblastoma, Theranostics. 2020 Jan 1;10(3):1355-1372. doi: 10.7150/thno.38147.
15. Gabryelska M., Wyszko E., Nowak S., Żukiel R., Barciszewski J., Zastosowanie medycyny molekularnej w terapii glejaków, Neuroskop, 2007, nr 9, 51-61.
16. W. Yu. M., F. Quail D., Immunotherapy for Glioblastoma: Current Progress and Challenges, Front Immunol. 2021; 12, doi: 10.3389/fimmu.2021.676301.
17. Stec R., Bodnar L., Smoter M., Szczylik C., Bewacizumab plus irinotekan w leczeniu nawrotowych glejaków mózgu, Współczesna Onkologia (2010) vol. 14; 4 (253–258). DOI: 10.5114/wo.2010.14433.
18. Kim, Michelle M., Umemura, Yoshi, Leung, Denise, Bevacizumab and Glioblastoma Past, Present, and Future Directions, The Cancer Journal 24(4):p 180-186, 7/8 2018. | DOI: 10.1097/PPO.0000000000000326.
19. Wojtukiewicz M. Z., Rybałtowski M., Sierko E., Podstawy biologiczne terapii ukierunkowanej na receptor czynnika wzrostu naskórka (EGFR), NOWOTWORY Journal of Oncology, 2008, volume 58, Number 3, 260–271.
20. Barker F. G., Simmons M. L., Chang S. M., Prados M. D., Larson D. A., Sneed P. K., Wara W. M., Berger M. S., Chen P., Israel M. A., Aldape K. D., EGFR overexpression and radiation response in glioblastoma multiforme, International Journal of Radiation Oncology*Biology*Physics Volume 51, Issue 2, 1 October 2001, Pages 410-418.
21. Raizer J. J., HER1/EGFR tyrosine kinase inhibitors for the treatment of glioblastoma multiforme, Journal of Neuro-Oncology, 74, pages 77–86 (2005).
22. Kierasińska A., Ciunowicz D., Węgierska M., Stoczyńska-Fidelus E., Rieske P., Terapia CAR-T w onkologii i w innych dziedzinach medycyny, Alergologia Polska – Polish Journal of Allergology 2021; 8, 2: 77–91.
23. Maggs L., Cattaneo G., Emre Dal A., Sanjari Moghaddam A., Ferrone S., CAR T Cell-Based Immunotherapy for the Treatment of Glioblastoma, Front Neurosci. 2021 May 25;15:662064. Doi: 10.3389/fnins.2021.662064.
24. Pant A., Lim M., CAR-T Therapy in GBM: Current Challenges and Avenues for Improvement, Cancers (Basel), 2023 Feb 16;15(4):1249. Doi: 10.3390/cancers15041249.
25. Wojtacki J., Lammek K., Skowrońska E., "After-hours" emergencies in patients under homecare – preliminary report, Medycyna Paliatywna, 2020 12(2): 66–74. Doi: https://doi.org/10.5114/pm.2020.97244.