WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 8, 252-265. Review Article ISSN 2277– 7105

A REVIEW ON THE TREATMENT OF BRAIN TUMOR BY ZIKA VIRUS

Rituraj Verma*, Madhuri Pandole and Sailesh Narayan

Radharaman College of Pharmacy, Ratibad, Bhopal (M.P.).

Article Received on
20 Feb. 2018,
Revised on 12 March 2018,
Accepted on 04 April 2018
DOI: 10.20959/wjpr20188-11803

***Corresponding Author**
Rituraj Verma
Radharaman College of Pharmacy, Ratibad, Bhopal (M.P.).

ABSTRACT

Zika virus used to treat aggressive brain cancer. The Zika virus was first discovered in 1947. The virus, spread by mosquitoes, rarely causes serious problems in adults but it can lead to birth defects, specifically microcephaly (a small, not fully developed head), if a woman contracts the virus when pregnant. The virus has the ability to cross the Blood Brain Barrier. Glioblastoma is hard to eradicate with conventional treatments because the stem cells that drive the growth of the cancer tend to recur after the more developed cancer cells are killed by chemotherapy or removed surgically. Average survival is only two years after diagnosis. Using Zika virus to treat glioblastoma has only been researched in cultured cells and tissue in the laboratory, as well as in mice. Glioblastoma is a highly lethal brain cancer that frequently recurs in proximity to the original resection cavity. We explored the use of oncolytic virus therapy against glioblastoma with Zika virus (ZIKV), a flavivirus that induces cell death and differentiation of neural precursor cells in the developing fetus. ZIKV preferentially infected and killed glioblastoma stem cells (GSCs) relative to differentiated tumor progeny or normal neuronal cells. The effects against GSCs were not a general property of neurotropic flaviviruses, as West Nile virus indiscriminately killed both tumor and normal neural cells. ZIKV potently depleted patient-derived GSCs grown in culture and in organoids.

KEYWORDS: Zika Virus (ZIKV), Glioblastoma stems cells (GSCs), Microencephaly, , neurotropic flaviviruses, Chemotherapy.

INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread to other parts of the body. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements. While these symptoms may indicate cancer.

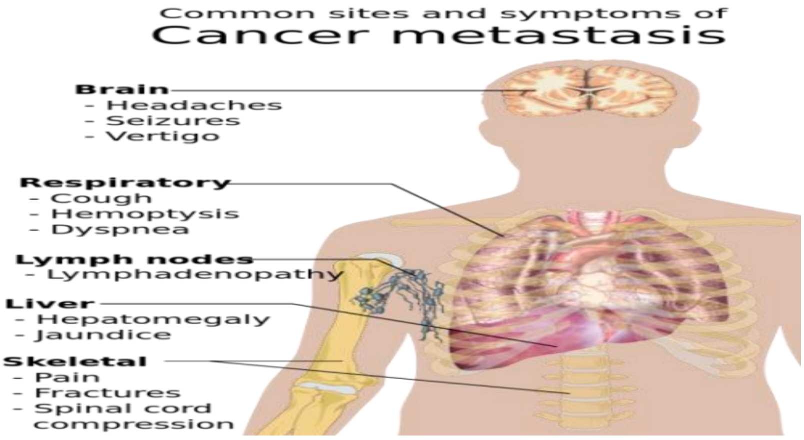
CLASSIFICATION

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

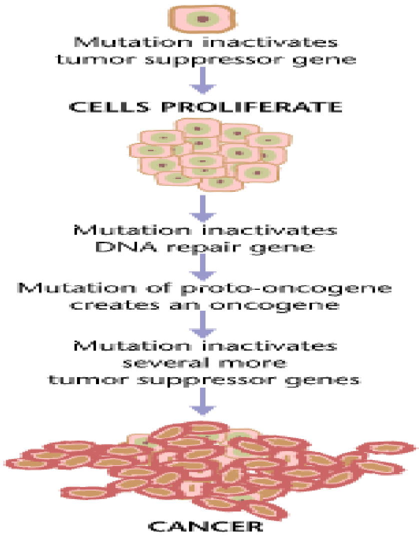
- Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.
- Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow.
- Lymphoma and leukemia: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.
- Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).
- Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue.

Cancers are usually named using -carcinoma, -sarcoma or -blastoma as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root. For example, cancers of the liver parenchyma arising from malignant epithelial cells is called hepatocarcinoma, while a malignancy arising from primitive liver precursor cells is called a hepatoblastoma and a cancer arising from fat cells is called a liposarcoma. For some common cancers, the English organ name is used. For example, the most common type of breast cancer is called ductal carcinoma of the breast. Here, the adjective ductal refers to the appearance of cancer under the microscope, which suggests that it has originated in the milk ducts.

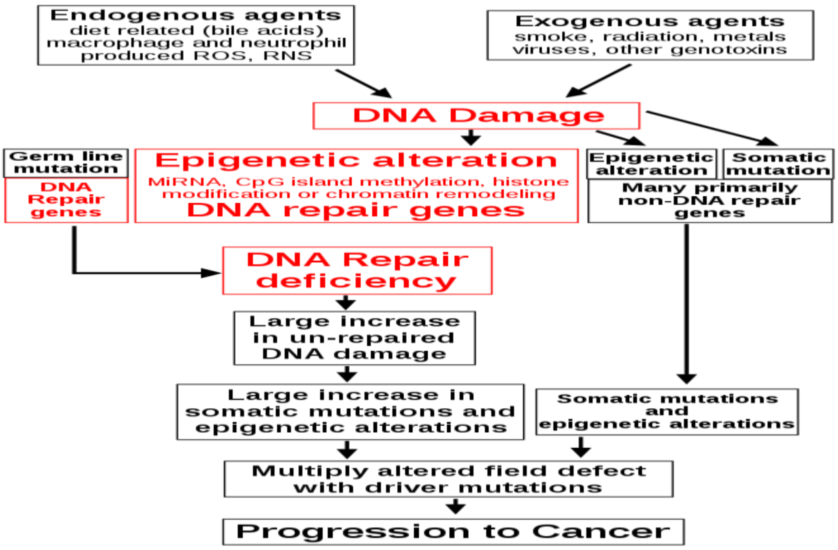
Benign tumors (which are not cancers) are named using -oma as a suffix with the organ name as the root. For example, a benign tumor of smooth muscle cells is called a leiomyoma (the common name of this frequently occurring benign tumor in the uterus is fibroid). Confusingly, some types of cancer use the -noma suffix, examples including melanoma and seminoma.



Symptoms of cancer metastasis depend on the location of the tumor.



Cancers are caused by a series of mutations.



The central role of DNA damage and epigenetic defects in DNA repair genes in carcinogenesis.

Brain Cancer

A brain tumor occurs when abnormal cells form within the brain. There are two main types of tumors: malignant or cancerous tumors and benign tumors. Cancerous tumors can be divided into primary tumors that start within the brain, and secondary tumors that have spread from somewhere else, known as brain metastasis tumors. All types of brain tumors may produce symptoms that vary depending on the part of the brain involved. These symptoms may include headaches, seizures, problem with vision, vomiting, and mental changes.[1] The headache is classically worse in the morning and goes away with vomiting. More specific problems may include difficulty in walking, speaking, and with sensation. As the disease progresses unconsciousness may occur.

The cause of most brain tumors is unknown. Uncommon risk factors include inherited neurofibromatosis, exposure to vinyl chloride, Epstein–Barr virus, and ionizing radiation. The evidence for mobile phones is not clear. The most common types of primary tumors in adults are meningiomas (usually benign), and astrocytomas such as glioblastomas. In children, the most common type is a malignant medulloblastoma. Diagnosis is usually by medical examination along with computed tomography or magnetic resonance imaging. This is then often confirmed by a biopsy. Based on the findings, the tumors are divided into different grades of severity.

Treatment may include some combination of surgery, radiation therapy, and chemotherapy. Anticonvulsant medication may be needed if seizures occur. Dexamethasone and furosemide may be used to decrease swelling around the tumor. Some tumors grow gradually, requiring only monitoring and possibly needing no further intervention.[1] Treatments that use a person's immune system are being studied. Outcome varies considerably depending on the type of tumor and how far it has spread at diagnosis. Glioblastomas usually have poor outcomes while meningiomas usually have good outcomes. The average five-year survival rate for brain cancer in the United States is 33%.

Secondary or metastatic brain tumors are more common than primary brain tumors, with about half of metastases coming from lung cancer. Primary brain tumors occur in around 250,000 people a year globally, making up less than 2% of cancers.[3] In children younger than 15, brain tumors are second only to acute lymphoblastic leukemia as the most common form of cancer.[8] In Australia the average lifetime economic cost of a case of brain cancer is $1.9 million, the greatest of any type of cancer.

Signs and Symptoms

The signs and symptoms of brain tumors are broad. People with brain tumors will experience them no matter if the tumor is benign (not cancerous) or cancerous. Primary and secondary brain tumors present with similar symptoms, with symptoms depend on the location, size, and rate of growth of the tumor. For example, larger tumors in the frontal lobe can cause changes in the ability to think. However, a smaller tumor in an area such as Wernicke's area (small area responsible for language comprehension) can result in a greater loss of function.

Intracranial pressure is usually the first sign of a brain tumor and it can cause persistent headaches.[2,3] These headaches may not respond to headache remedies and they may be accompanied by vomiting.[2]

The brain is divided into 4 lobes and each lobe or area has its own function. A tumor in any of these lobes may affect the area's performance. The location of the tumor is often linked to the symptoms experienced but each person may experience something different. Frontal lobe tumors may contribute to poor reasoning, inappropriate social behavior, personality changes, poor planning, lower inhibition, and decreased production of speech (Broca's area).

Temporal lobe: Tumors in this lobe may contribute to poor memory, loss of hearing, difficulty in language comprehension (Wernicke's area).

Parietal lobe: Tumors here may result in poor interpretation of languages, decreased sense of touch and pain, and poor spatial and visual perception.

Occipital lobe: Damage to this lobe may result in poor or loss of vision.

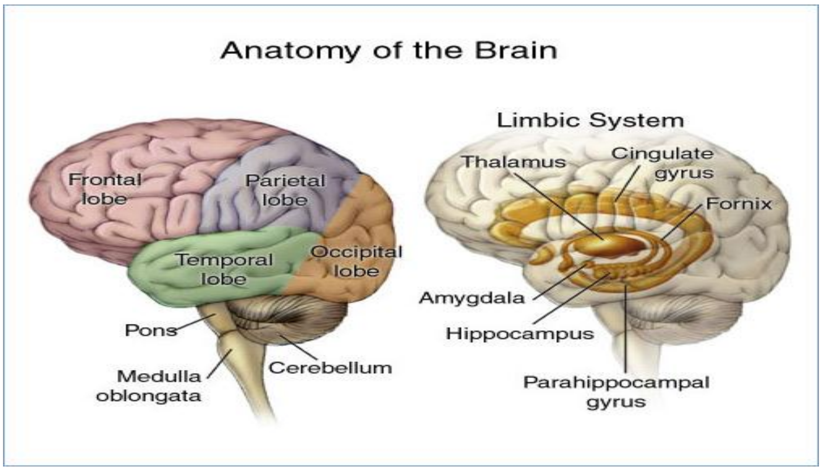
Cerebellum: Tumors in this area may cause poor balance, muscle movement, and posture.

Brain stem: Tumors on this can affect blood pressure, swallowing, and heartbeat.

Behavior Changes

Despite the personality and behavior changes that occur in people with brain tumors, little research on such changes has been done. A person's personality may be altered due to the tumor damaging lobes of the brain. Since the frontal, temporal, and parietal lobes control inhibition, emotions, mood, judgement, reasoning, and behavior, a primary or secondary tumor in that region can cause inappropriate social behavior, temper tantrums, laughing at things which merit no laughter,[3] and even psychological symptoms such as depression and anxiety.

Personality changes can have damaging effects such as unemployment, unstable relationships, and a lack of control.

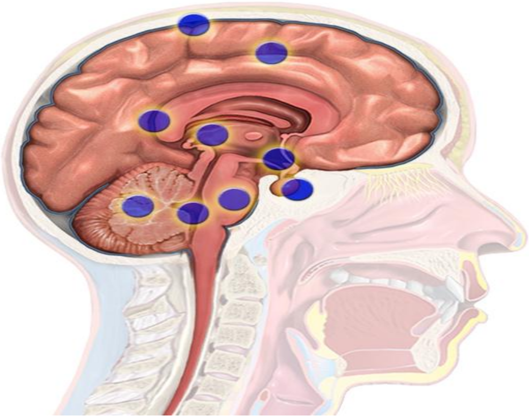


The main areas of the brain and limbic system.

Cause

Epidemiological studies are required to determine risk factors.[4] Aside from exposure to vinyl chloride or ionizing radiation, there are no known environmental factors associated with brain tumors. Mutations and deletions of so-called tumor suppressor genes, such as P53, are thought to be the cause of some forms of brain tumor.[5] Inherited conditions, such as Von Hippel–Lindau disease, multiple endocrine neoplasia, and neurofibromatosis type 2 carry a high risk for the development of brain tumors.[6,7] People with celiac disease have a slightly increased risk of developing brain tumors.[8]

Although studies have not shown any link between cell phone or mobile phone radiation and the occurrence of brain tumors,[9] the World Health Organization has classified mobile phone radiation on the IARC scale into Group 2B – possibly carcinogenic.[10] Discounting claims that current cell phone usage may cause brain cancer, modern, third-generation (3G) phones emit, on average, about 1% of the energy emitted by the GSM (2G) phones that were in use when epidemiological studies that observed a slight increase in the risk for glioma – a malignant type of brain cancer – among heavy users of wireless and cordless telephones were conducted.



Brain cancer regions.

Classification

Secondary Brain Tumors: Secondary tumors of the brain are metastatic and have invaded the brain from cancers originating in other organs. This means that a cancerous neoplasm has developed in another organ elsewhere in the body and that cancer cells have leaked from that primary tumor and then entered the lymphatic system and blood vessels. They then circulate through the bloodstream, and are deposited in the brain. There, these cells continue growing and dividing, becoming another invasive neoplasm of the primary cancer's tissue. Secondary tumors of the brain are very common in the terminal phases of patients with an incurable metastasized cancer; the most common types of cancers that bring about secondary tumors of the brain are lung cancer, breast cancer, malignant melanoma, kidney cancer, and colon cancer (in decreasing order of frequency).

Secondary brain tumors are more common than primary ones; in the United States there are about 170,000 new cases every year. Secondary brain tumors are the most common cause of tumors in the intracranial cavity. The skull bone structure can also be subject to a neoplasm that by its very nature reduces the volume of the intracranial cavity, and can damage the brain.

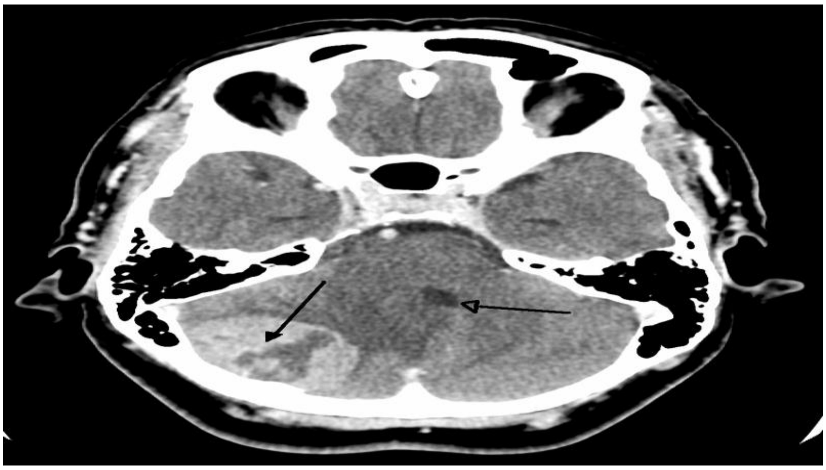
Behavioral Changes: Brain tumors or intracranial neoplasms can be cancerous (malignant) or non-cancerous (benign). However, the definitions of malignant or benign neoplasms differ from those commonly used in other types of cancerous or non-cancerous neoplasms in the body. In cancers elsewhere in the body, three malignant properties differentiate benign tumors from malignant forms of cancer: benign tumors are self-limited and do not invade or metastasize. Characteristics of malignant tumors include.

- Uncontrolled mitosis (growth by division beyond the normal limits)
- Anaplasia: the cells in the neoplasm have an obviously different form (in size and shape). Anaplastic cells display marked pleomorphism. The cell nuclei are characteristically extremely hyperchromatic (darkly stained) and enlarged; the nucleus might have the same size as the cytoplasm of the cell (nuclear-cytoplasmic ratio may approach 1:1, instead of the normal 1:4 or 1:6 ratio). Giant cells – considerably larger than their neighbors – may form and possess either one enormous nucleus or several nuclei (syncytia). Anaplastic nuclei are variable and bizarre in size and shape.
- invasion or infiltration (medical literature uses these terms as synonymous equivalents. However, for clarity, the articles that follow adhere to a convention that they mean slightly different things; this convention is not followed outside these articles):
- Invasion or invasiveness is the spatial expansion of the tumor through uncontrolled mitosis, in the sense that the neoplasm invades the space occupied by adjacent tissue, thereby pushing the other tissue aside and eventually compressing the tissue. Often these tumors are associated with clearly outlined tumors in imaging.
- Infiltration is the behavior of the tumor either to grow (microscopic) tentacles that push into the surrounding tissue (often making the outline of the tumor undefined or diffuse) or to have tumor cells "seeded" into the tissue beyond the circumference of the tumorous mass; this does not mean that an infiltrative tumor does not take up space or does not compress the surrounding tissue as it grows, but an infiltrating neoplasm makes it difficult to say where the tumor ends and the healthy tissue starts.
- metastasis (spread to other locations in the body via lymph or blood).

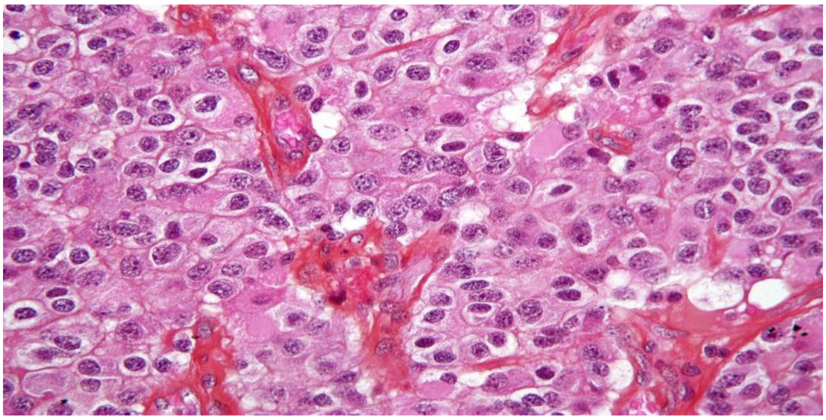
Of the above malignant characteristics, some elements do not apply to primary neoplasms of the brain:

- Primary brain tumors rarely metastasize to other organs; some forms of primary brain tumors can metastasize but will not spread outside the intracranial cavity or the central spinal canal. Due to the BBB, cancerous cells of a primary neoplasm cannot enter the bloodstream and get carried to another location in the body. (Occasional isolated case reports suggest spread of certain brain tumors outside the central nervous system, e.g. bone metastasis of glioblastoma multiforme.)
- Primary brain tumors generally are invasive (i.e. they will expand spatially and intrude into the space occupied by other brain tissue and compress those brain tissues); however, some of the more malignant primary brain tumors will infiltrate the surrounding tissue.

Of numerous grading systems in use for the classification of tumor of the central nervous system, the World Health Organization (WHO) grading system is commonly used for astrocytoma. Established in 1993 in an effort to eliminate confusion regarding diagnoses, the WHO system established a four-tiered histologic grading guideline for astrocytomas that assigns a grade from 1 to 4, with 1 being the least aggressive and 4 being the most aggressive.



A posterior fossa tumor leading to mass effect and midline shift.



Micrograph of an oligodendroglioma, a type of brain cancer. Brain biopsy. H&E stain.

Zika Virus

Introduction

Zika virus is a mosquito-borne flavivirus that was first identified in Uganda in 1947 in monkeys through a network that monitored yellow fever. It was later identified in humans in 1952 in Uganda and the United Republic of Tanzania. Outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia and the Pacific. From the 1960s to 1980s, human infections were found across Africa and Asia, typically accompanied by mild illness. The first large outbreak of disease caused by Zika infection was reported from the Island of Yap

(Federated States of Micronesia) in 2007. In July 2015 Brazil reported an association between Zika virus infection and Guillain-Barré syndrome. In October 2015 Brazil reported an association between Zika virus infection and microcephaly.

Signs and Symptoms

The incubation period (the time from exposure to symptoms) of Zika virus disease is not clear, but is likely to be a few days. The symptoms are similar to other arbovirus infections such as dengue, and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms are usually mild and last for 2-7 days.

Complications of Zika Virus Disease

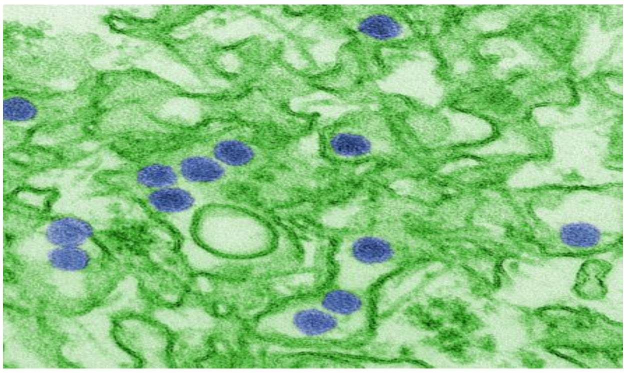
Based on a systematic review of the literature up to 30 May 2016, WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly; and that Zika virus is a trigger of Guillain-Barré syndrome. Intense efforts are continuing to investigate the link between Zika virus and a range of neurological disorders, within a rigorous research framework.

Transmission

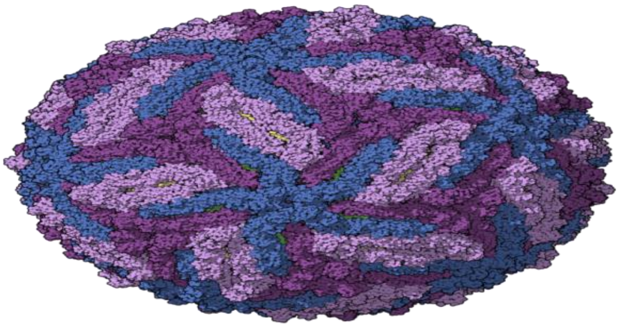
Zika virus is primarily transmitted to people through the bite of an infected mosquito from the Aedes genus, mainly Aedes aegypti in tropical regions. Aedes mosquitoes usually bite during the day, peaking during early morning and late afternoon/evening. This is the same mosquito that transmits dengue, chikungunya and yellow fever. Sexual transmission of Zika virus is also possible. Other modes of transmission such as blood transfusion are being investigated.

Diagnosis

Infection with Zika virus may be suspected based on symptoms and recent history of travel (e.g. residence in or travel to an area with active Zika virus transmission). A diagnosis of Zika virus infection can only be confirmed through laboratory tests on blood or other body fluids, such as urine, saliva or semen.



This is a digitally-colorized transmission electron micrograph (TEM) of Zika virus, which is a member of the family Flaviviridae. Virus particles, here colored blue, are 40 nm in diameter, with an outer envelope, and an inner dense core.



Zika virus capsid, colored per chains.

Cross-section of Zika virus, showing the viral envelope composed of envelope proteins (red) and membrane proteins (purple) embedded in the lipid membrane (white).The capsid proteins (orange) are shown interacting with the RNA genome (yellow) at the center of the virus.

Zika Virus Used to Treat Aggressive Brain Cancer: There are many different types of brain cancer where Glioblastomas are the most common, fast growing and diffuse making it difficult to distinguish between the tumour and healthy tissue in adults.

Radiotherapy, chemotherapy and surgery is not enough to remove these invasive cancers.

According to the latest researches, in living mice and donated human brain tissue samples, shows Zika therapy can kill cells that tend to be resistant to current treatments.

The glioblastoma stem cells continue to grow and divide, producing new tumour cells even after aggressive medical treatment.

Adult brains have very few stem cells this ensures Zika treatment should destroy only the cancer-causing brain stem cells without causing much collateral damage.

According to the Zhe Zhu, Zika virus might be able to infect and kill glioblastoma cell.

According to the researcher Dr. Michael Diamond and Dr. Milan Chheda from Washington University School Of Medicine in St. Louis and Dr. Jeremy Rich from University of California School of Medicine in San Diego stated that Zika virus is selectively targeted neuroprogenitor or stem cell in the brain of developing fetus might be able to infect and kill glioblastoma cell especially that are hard to eradicate.

The virus would need to be delivered directly to where it is needed in the brain.

CONCLUSION

This is very much a "proof of concept" study, and tests on cells, tissues and mice don't necessarily translate into a safe and effective treatment for humans. The study has several limitations, but the fact the treatment so far hasn't been tested on humans is the most important. For one thing, Zika virus doesn't naturally infect mice, so researchers had to use a specially engineered virus that's different from the virus that infects humans.

Also, the glioma tumours in mice were taken from mouse models, so they weren't the same as human glioma tumours. The researchers say there are "technical challenges" to overcome before they can test human-derived glioma cells in mice.

They say it may be possible to make the Zika virus safe enough to use in glioma treatment, possibly by injecting it into tumour sites at the same time as surgery to remove tumours.
But clinical trials of such a therapy are still some way off.

REFERENCES

1. Longo, Dan L. "369 Seizures and Epilepsy". Harrison's principles of internal medicine (18th ed.). McGraw-Hill. 2012; 3258. ISBN 978-0-07-174887-2.
2. Kahn, Kevin; Finkel, Alan. "It IS a tumor -- current review of headache and brain tumor". Current Pain and Headache Reports, June 2014; 18(6): 421. doi:10.1007/s11916-014-0421-8. ISSN 1534-3081. PMID 24760490.
3. Gregg, N. (2014). ""Neurobehavioural Changes In Patients Following Brain Tumour: Patients And Relatives Perspective."". Supportive Care in Cancer.
4. Jones, Caleb. "Brain Tumor Symptoms | Miles for Hope | Brain Tumor Foundation". milesforhope.org. Archived from the original on 14 August 2016. Retrieved 3 August 2016.
5. Krishnatreya, M; Kataki, AC; Sharma, JD; Bhattacharyya, M; Nandy, P; Hazarika, M. "Brief descriptive epidemiology of primary malignant brain tumors from North-East India". Asian Pacific Journal of Cancer Prevention, 2014; 15(22): 9871–73. doi:10.7314/apjcp.2014.15.22.9871. PMID 25520120.
6. Kleihues P, Ohgaki H, Eibl RH, Reichel MB, Mariani L, Gehring M, Petersen I, Höll T, von Deimling A, Wiestler OD, Schwab M. "Type and frequency of p53 mutations in tumors of the nervous system and its coverings". Molecular Neuro-oncology and Its Impact on the Clinical Management of Brain Tumors. Recent results in cancer research. 135. Springer, 1994; 25–31. ISBN 3540573518.
7. Hodgson TS, Nielsen SM, Lesniak MS, Lukas RV. "Neurological Management of Von Hippel-Lindau Disease". Neurologist (Review). 2016; 21(5): 73–78. doi:10.1097/NRL.0000000000000085. PMID 27564075.
8. Rogers L, Barani I, Chamberlain M, Kaley TJ, McDermott M, Raizer J, et al. "Meningiomas: knowledge base, treatment outcomes and uncertainties. A RANO

review". J Neurosurg (Review), 2015; 122(1): 4–23. doi:10.3171/2014.7.JNS131644. PMC 5062955 Freely accessible. PMID 25343186.

9. Hourigan CS. "The molecular basis of coeliac disease". Clin Exp Med (Review), 2006; 6(2): 53–59. doi:10.1007/s10238-006-0095-6. PMID 16820991.
10. Frei P, Poulsen AH, Johansen C, Olsen JH, Steding-Jessen M, Schüz J (19 October 2011). "Use of mobile phones and risk of brain tumours: update of Danish cohort study". BMJ. 343: d6387. doi:10.1136/bmj.d6387. PMC 3197791.