Usage of Nanoparticles in Treating Pediatric Glioblastoma

Sharvari Deshpande[+], Rajagopal Appavu*
[+]dsharvari2020@gmail.com; *drraj@researchrisingstars.com
[+]Woodbridge Academy Magnet School, 1 Convery Blvd, Woodbridge, NJ 07095
*Research Rising Stars, Tampa, FL 33647

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ABSTRACT

As cancer continues to be the second leading cause of death in the world today, treating it as effectively as possible is an important goal to achieve. Among the various types of cancers, brain cancer, specifically aggressive brain cancer known as glioblastoma, is difficult to treat with current treatment options due to the nature and location of the tumor. While not common in pediatrics, it has significantly low survival rates upon diagnosis. To increase the efficiency of treatments, nanotechnology, such as the use of nanoparticles to treat and diagnose this cancer, is being researched with various types of nanoparticles and drug delivery being explored for the most effective and least invasive and damaging treatment regimens.

1. Introduction to Pediatric Glioblastoma

1.1. What is pediatric glioblastoma

Glioblastoma is a common form of cancer seen in adults, while only about 3% of childhood brain tumors are glioblastoma.[1] While brain cancer is one of the most common forms of pediatric cancer, glioblastoma is not. Since glioblastoma is a rare occurrence in pediatric patients, there is no clear treatment outline for children with glioblastoma, but rather treatment for adult glioblastoma is used as a blueprint.[2] Still, the World Health Organization deemed that while the histology of adult and pediatric brain cancer is similar, they are two different types of cancers due to their epigenetics and landscape.

Glioblastoma, or childhood glioblastoma multiforme, is an aggressive form of brain cancer that affects the glial cells in the central nervous system. The central nervous system of humans is composed of two types of cells, neurons, which are the cells that relay neural impulses throughout the body, and glial cells, which are supportive cells that aid neurons. Glioblastoma is usually seen in children between the ages of 5 to 9.[3]

Oftentimes, the tumor is located in areas of the brain involved in speech, movement, thinking processes, temperature and sensation perceptions, balance, and motor coordination.

Headaches, nausea, weakness on one side of the body, deterioration of eyesight, fatigue in the morning, motor dysfunction, hormone abnormalities, differences in behavior and thinking, and seizures (depending on the location of tumors) are noted. These symptoms can have a sudden onset or develop slowly. The main symptoms based on cases studied appear to be vomiting and persistent headaches.

Survival prognosis for this form of cancer is also significantly lower than other forms of cancer due to its nature, but various interventions can increase survival rates slightly and can help remove portions of the tumor.

1.2. Current Treatments

When treating pediatric glioblastoma, there is no set protocol outlining treatment, but it involves surgery, radiation, and chemotherapy, all of which have their own pros and cons.-

Many available treatment options to improve the outlook of drug performance are invasive procedures that have their own set of risks. Currently, there are a handful of treatments that are in use and being tested.

Intraventricular infusion is the process in which medication (in this case the cancer treatment) is injected into the fluid-filled cavities in the brain.[5]

Convection- enhanced treatments involve infusing the drug directly into the tumor itself by creating a small hole in the skull and inserting a cannula into it.[6]

An intracerebral implant involves small devices being placed near a tumor that releases medication in small bursts.

Intrathecal chemotherapy is a treatment where the medications in chemotherapy are inserted into the cerebrospinal fluid that

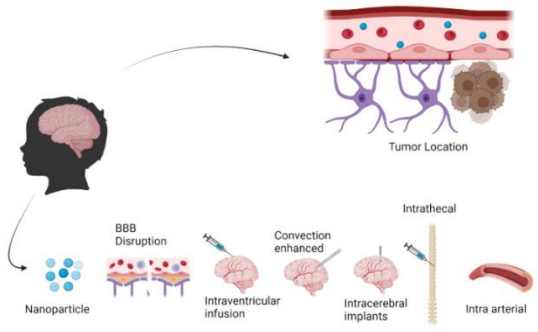

Figure 1: Methods of Glioblastoma Treatments (Created with Biorender)

circulates around the spinal cord during a lumbar puncture.[7]

Lastly, intra-arterial treatment involves inserting medication into the arteries that are directly supporting the tumor.

Of these treatments, many of them are often excessively invasive, and can cause damage to the patient both physically and emotionally; these invasive treatments are not best suited for pediatric patients.

1.2.1. Surgery

Surgery, or neurosurgery, is the first step to treat glioblastoma (or is sometimes done after a preceding dose of radiation therapy to shrink the tumor first). If the location of the tumor is operable, then once the tumor is identified, tumor resectioning will occur. While the ideal goal is to remove the entire tumor, the nature of the tumor makes it difficult to do so, as it invades healthy brain tissue. In cases like these, the surgery is done to remove as much of the tumor as possible without damaging the surrounding brain structure.

To increase the efficiency and effectiveness of tumor resectioning, surgeons perform intraoperative MRI surgery, in which they use MRI images to guide them throughout the surgery to remove as much of the tumor as possible without damaging healthy brain structures and tissue.

1.2.2. Radiation

Following surgery, radiation therapy is administered, which involves high doses of radiation to target a specific location to shrink a tumor. This is typically post-operation as it works to remove the remaining tumor or

cancer cells that were left behind while performing surgery; it increases the survival rates of patients.[8]

Yet, while this therapy is beneficial in treating the tumor, it negatively impacts pediatric patients by affecting their thinking and memory processes and causing problems learning in school and behaving. Additionally, it can cause seizures and result in the death of neurons (necrosis).

1.2.3. Chemotherapy

Chemotherapy is also given to pediatric glioblastoma patients following surgery and/or radiation therapy. Chemotherapy is a combination of drugs and chemicals that destroy all cells. It is used before surgery in some cases to attempt to shrink the tumor before it is removed. But research does not show that it is beneficial in treating glioblastoma, or that it aids in increasing the survival rate for pediatric patients.

Additionally, while crossing the blood-brain barrier (Figure 3) the drugs tend to be filtered out and very little of the actual medication reaches the tumor, making it less effective than other treatments.

1.3. Nanoparticle Introduction for Pediatric Glioblastoma

Due to the lack of beneficial available treatments and the large amount of side effects of current medical interventions, the usage of nanoparticles to treat pediatric glioblastoma is on the rise.

In the medical field, nanotechnology has been on the rise to treat a variety of problems, including many cancers and neurological diseases, and diagnose certain diseases/disorders.

The application of nanoparticles to pediatric glioblastoma will allow for effective treatments, and as further research continues, fewer side effects and increased survival rates.

Nanoparticles are particles that have at least one side with dimensions less than 100 nm overall.[9] In comparison to other structures in the body, they are much smaller (Figure 2). For example, nanoparticles are smaller than the red blood cells in our bodies.

Nanoparticles spread through the gaps in the human body can directly affect certain cell structures or tissues and are able to circulate through the body undetected based on their makeup due to their small size and compounds.

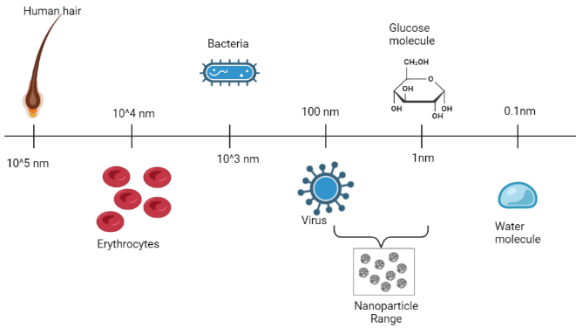

Figure 2: Nanoparticle Size Comparison

Since glioblastoma occurs in the brain, in order to have drugs circulate into the brain, they need to cross the blood-brain barrier (BBB) and not be filtered out by it. Many medications are mostly filtered out by the BBB and are not able to treat brain tumors with effective volumes of medications.

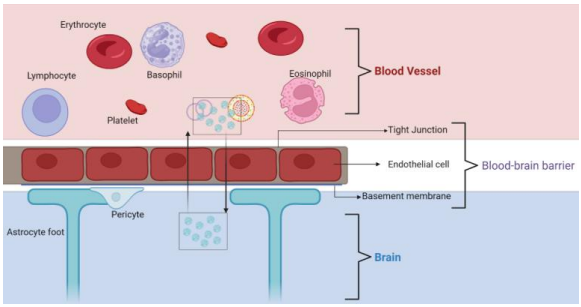

Figure 3: Diagram of the Blood-Brain Barrier; shows major components that make up the barrier and where they are located

The BBB is a membrane between blood vessels and the brain that filters out toxic substances from the bloodstream, protects the brain from harmful toxins, and provides nutrients to the brain. It is composed of various blood vessels and astrocytes (a type of glial cell that makes up the majority of the central nervous system glia).[10] It allows the passages of specific molecules only, making it semi-permeable to lipid soluble molecules and low-weight positively charged molecules through diffusion, membrane transport, pumps, transcytosis, and carrier-mediated transport. This results in many molecules being filtered out, including medications.[11]

2. Formulation of Nanoparticles

Through modification of nanoparticles, specific surface properties can allow nanoparticles to pass through the BBB and into the brain to treat the tumor and effectively release large volumes of drug into the system. In order to do this, specific nanoparticles require specific properties, hence the formulation of nanoparticles is tedious and requires various applications of chemistry, biology, and physiological understanding.

2.1. Inorganic Nanoparticles Formulation

Most inorganic nanoparticles have a solid core that is magnetic or metallic to some extent. Iron (II, III) oxide nanoparticles are one of the most commonly used nanoparticles for imaging due to their properties. It has an iron core that was reduced in an inert atmosphere at high temperatures with reactive oxygen. The core is then capped with a ligand or is directly mixed with a hydrophilic ligand before further modifications to the basic structure.[12]

Another method of forming inorganic nanoparticles is through coprecipitation methods which involves the precipitation of metal ions with counterions in a solution until the nanoparticle core is formed.

In coprecipitation, soluble reactants are to form a precipitate in certain conditions. When supersaturation occurs of these soluble reactants, nucleation- the process of atoms forming a crystalline solid-like pattern[13] - occurs.[14]

Metallic nanoparticle formulation occurs in a similar manner. The metallic core is formed first and then is capped with a ligand before being modified to with more specific properties depending on its required function.

2.2. Organic Nanoparticle Formulation

The formulation of organic nanoparticles takes place in an aqueous environment which results in ‘soft’ particles that have a flexible but solid structure. Organic nanoparticles are typically synthesized through materials that are commercially available, but polymers are used to further modify them, one such polymer being PEG.[15]

PEG stands for polyethylene glycol and serves to increase the half-life of organic nanoparticles allowing them to remain in the bloodstream for longer.[16]

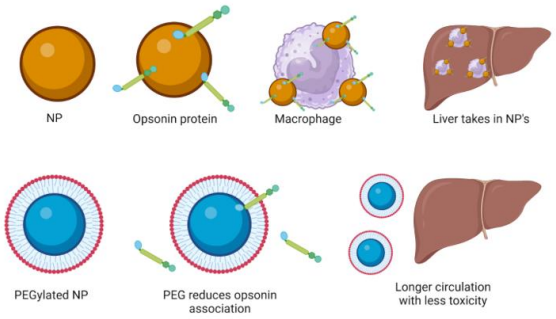

Figure 4: PEGylated NPs (Created with Biorender)

3. Applications of Nanoparticles

3.1. Introduction to Applications

Nanoparticles are not only used to treat brain cancers but also have applications in diagnosing and scanning the brain for brain cancer. Diagnostic nanoparticles, therapeutic nanoparticles, and theranostic nanoparticles are three different types of nanoparticles that are being researched and studied through clinical trials. Diagnostic nanoparticles are used to highlight tumors through magnetic resonance imaging and dyes, therapeutic nanoparticles are used to encapsulate drugs and deliver them to the brain tumor locations, and theranostics are a combination of both and contain nanoparticles that deliver drugs but have the ability to produce scans of tumors. Solid-inorganic, organic, semiconductor quantum dots and polymer nanoparticles are all used, but each is used in a distinct manner.

Nanoparticles can perform a wide variety of functions, but depending on the type of nanoparticle, they have their strengths and weaknesses. For example, some nanoparticles are better at delivering drugs through both active and passive methods, while others are better at increasing the retention of the drug in tumors, or have a higher half-life and allow the drug to stay in the body for longer. Due to their various properties, nanoparticles are preferred in certain situations. Many methods that are being tested have the potential to work in the human brain/body, yet issues with toxicity are a major aspect that is yet to be fully understood before the nanoparticles can be approved for use in humans.

3.2. Diagnostic Applications

Diagnostic nanoparticles work as contrast dyes and work with scans on magnetic resonance imaging technology (MRIs); these dyes, when exposed in the body are absorbed by brain tumors and outline the general shape of the tumor. These scanning nanoparticles are useful when it comes to monitoring the growth and reduction of a brain tumor in addition to aiding in intraoperative surgery of the brain. Mostly, inorganic nanoparticles are used for this, and the majority of them have the ability to transport gadolinium, a contrast dye.

3.2.1. Gadolinium chelates

The best functioning nanoparticles for MRI diagnostics are the gadolinium chelates, which contain gadolinium (III) ion; due to its high magnetic movement, it acts as a high-functioning contrast dye to use with MRIs. While these nanoparticles contain the best contrast dye, they also have the potential to allow for the gadolinium to leak out, and become absorbed in surrounding brain tissue. This can cause issues as the MRI will not be able to distinguish between brain tissue and the tumor, and can cause problems when performing surgery guided by MRI scans. The toxicity of this is yet to be understood as well.

3.2.2. Gold Nanoparticles

Fluorescent imaging technology through gold nanoparticles is also a technique to diagnose brain cancer. The nanoparticle

contains fluorescent imaging molecules and is used to view brain tumors.

3.2.3. Iron (II, III) oxide Nanoparticles

Similarly, Iron (II, III) oxide has the ability to increase absorption over time, and thus, this form of nanoparticle contrast dye can be injected 24 hours prior to brain surgery, and can still be used to scan for an MRI.

3.2.4. Quantum Dots

Quantum dots can also be used to deliver drugs to brain tumors, and through the use of phagocytosis, the drugs would be uptaken and provide an outline of the brain tumors in scans.

3.2.5. Other nanoparticles

Hydrogels can contain a blue dye called Coomassie Brilliant Blue, and have the ability to stain brain tumors and not the rest of the brain tissue, making the tumor visible, which is very important especially when it comes to applications of this nanoparticle in surgeries.

3.3. Therapeutic Applications

Therapeutic nanoparticles are used only to deliver drugs to the tumor and contain various medications that are included in chemotherapy. Nanoparticles that are for solely therapeutic purposes are either thermotherapy or contain chemotherapy drugs them that are released. Others are made to release infrared lighting to shrink the brain tumor.

The majority of these types of nanoparticles have the ability to perform thermotherapy, in which the nanoparticle releases heat that kills the cancer cells but does not damage the surrounding brain tissue, through various sources such as visible, infrared, or radio waves. Many polymer-based nanoparticles are able to carry chemotherapy drugs through the blood-brain barrier and to the site of the tumor.

3.4 Theranostic Applications

Theranostic nanoparticles have the ability to diagnose and treat brain tumors. Nanoparticles of this source are either able to act as contrast dye along with releasing drugs or have the ability to contain fluorescently tagged drugs; these allow for constant monitoring of the drugs and how they impact the brain tumor.

As mentioned earlier, iron (II, III) oxide and gold nanoparticles are both on their own diagnostic and therapeutic nanoparticles, but can also work as both due to their properties. Iron (II, III) oxide is a contrast dye that can encapsulate drugs while gold nanoparticles can contain fluorescently tagged drugs.

Through these three primary methods, nanoparticles are being used to treat and diagnose glioblastoma.

4. Delivery of Therapy:

The two main forms of therapy for cancer treatment involve active and passive delivery. Active delivery involves nanoparticles binding to antibodies at specific locations and producing heat to kill the cancer tumors, or to reach a specific location and then release the drugs it had encapsulated. Passive delivery involves using the weakened blood-brain-barrier to enter into the central nervous system, as when there is a tumor, the gaps between the vessels and neurons increase, allowing for nanoparticles to enter; additionally, some nanoparticles have the ability to release drugs when entering an area that has specific measurements in pH, oxygen levels, redox

potential, or due to ultrasound/magnetic waves.

4.1 Active Targeting

Active targeting strategies include activities trying to deliver drugs to a specific location; they tend to be more efficient and specific and try to release drugs in a specific environment at a (typically) slow and steady rate. They have a high volume of drugs that are able to treat the tumor and provide effective treatments.

4.1.1. Antibody-conjugated Nanoparticles

Active targeting with nanoparticles frequently involves the use of binding to ligands, specifically through the use of antibodies.[17] Antibodies are produced by B cells to bind to foreign substances that enter the body.[18] Antibodies bind to specific ligands, and this is exploited for the use of targeted drug therapy.[19]

Cancer occurs due to mutations or issues in many genes, one of which is tumor suppressor genes. These genes function to suppress the overproduction of cells, and promote apoptosis; when not functioning, they fail to limit the production of cells leading to cell inhibition, and the formation of cancer. There are many genes and surface markers that are expressed on tumors in addition to the cancer receptors that are overexpressed. Antibodies can be modified to specifically bind to any of these surface markers to cancer receptors for accurate drug targeting.

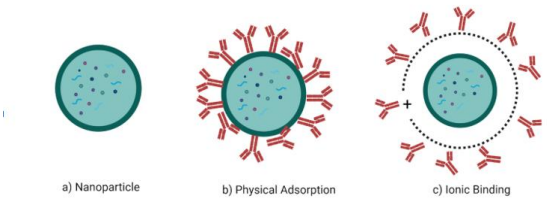

Figure 5: Antibodies (Created with Biorender)

There are various ways to conjugate antibodies to the surface of nanoparticles, primarily physical adsorption and ionic binding. Physical adsorption occurs when weak noncovalent hydrophobic electrostatic hydrogen bonding or Van der Waals interactions occur between the nanoparticles and the antibodies. Ionic binding occurs when the antibody and nanoparticles have opposite charges, and is a simple and less time-consuming process to carry out. In both cases, it is important that the modifications carried out to allow for the conjugation of the antibodies do not alter the binding ability of the antibody.

Once this is done and the antibody-conjugated nanoparticle has been created, it is released into the body; when a specific cancer receptor is recognized, the antibodies bind to it resulting in the nanoparticle passing through and releasing the drug at this specific cancer-located site.

Through this process, a high volume of chemotherapy drugs are introduced to a specific location to make treatment more efficient.

4.1.2. Receptor-Mediated Targeting

Specific cancer cells overexpress various receptors, which results in one more method for active targeting. Since certain tumor cells overexpress specific receptors, nanoparticles can be formulated to bind to these specific receptors.

When this occurs, the nanoparticle can enter the tumor and release the drugs it is carrying directly where the tumor is located. By binding directly to the tumors' receptors, the nanoparticle is able to access the tumor itself and release a high volume of medication directly at the tumor.

Specifically, folate acid (a nucleic acid vital to growth in cells) has receptors on all cells, but these receptors are highly overexpressed on the surface of particular cancer cells. Due to this, many cancer treatments are able to create nanoparticles that will bind to these overexpressed folate receptors. Depending on the type of cancer that is being treated, the exact folic acid receptor will vary between the alpha or beta receptor. The nanoparticle will then bond to the receptor and be able to directly deliver the drug to the tumor.

4.2 Passive Targeting

4.2.1. Enhanced Permeability and Retention (EPR) Effect

When drugs are injected into the bloodstream of a patient, intratumoral treatment is dependent mostly on blood vessels. In healthy patients, blood vessels are tightly sealed off with endothelium and supported. Due to this, medication cannot be circulated into specific areas and allowed to accumulate, rather the substances would be filtered out through the blood.[20]

When tumors become cancer, and metastasize, they envelope blood vessels in order to gather nutrients that they require to grow. Blood vessels of tumors are not structured the same as the blood vessels in healthy humans; tumor vasculature does not have a full endothelium seal on the blood vessels resulting in large pores forming in the lining of the blood vessels.

Nanoparticles have the ability to flow through the pores in the blood vessels and release drugs in tumors that accumulate and are retained since the blood vessels are not lined tightly enough to block or filter the medication. Passive transport exploits this phenomenon coined the enhanced permeability and retention effect to treat cancer.

While the EPR effect allows for drugs to more easily pass into tumors, the amount of time required to circulate drugs into the tumor through blood vessels can result in the loss of medication; therefore, nanoparticles need to have an increased half-life to be able to deliver a high volume of drugs to the tumor.

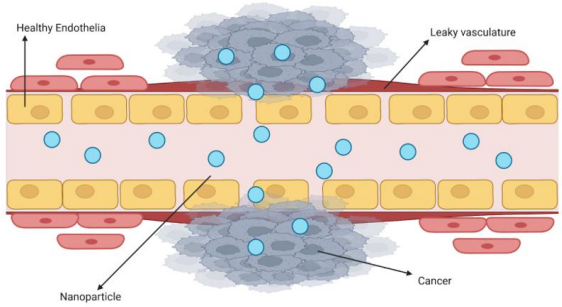

Figure 6: Enhanced Permeability and Retention Factor (Created with Biorender)

4.2.2. Tumor Microenvironment (TME)

Tumor cells are replicating rapidly, constantly performing glycolysis to keep up. Due to this, there is an increased acidic environment around tumor cells. This can be used, along with the EPR to deliver drugs through the regulated nanoparticles.[21]

Nanoparticles are formulated to recognize changes in their surrounding environment. The leaky vascular structure allows for the nanoparticle to enter the bloodstream and circulate around the body. When the nanoparticle reaches an environment that is

highly acidic (has a high pH) it releases the drugs in its system to the surrounding environment, where the tumor is located.

In this way, the TME allows for the recognition of the tumor and aids the nanoparticle to release medication passively; while not actively targeting the tumor, using this technology, the drug is still released in the surroundings of the tumor due to the acidic microenvironment the tumor produces.

5. Future

While the field of nanoparticles is only being explored currently, it will be further researched in the future as the abilities of technology expand, allowing for more advancements in the field of nanotechnology.

Many nanotechnology treatments including those that diagnose and those that treat are being tested in labs and through various clinical trials. With success in determining the side effects and toxicities of various nanoparticles, the presence of nanotechnology in oncology and the medical field in general will only expand.

6. Conclusion

While many of the outlined nanoparticle treatments and processes are currently being researched and tested, they are all at various stages in the approval process, with some being studied for potential while others are FDA-approved or part of clinical trials. Nanoparticles have the unique ability to be tailored to treat brain cancer and increase the amount of medication that is reaching the tumor in the brain that other drugs can not due to the blood-brain barrier. The use of nanoparticles to treat glioblastoma, especially in pediatric patients is important to medical treatments for this to continue to involve nanotechnology.

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