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Medulloblastoma, Childhood Cancer

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Abstract

Medulloblastoma is the most common malignant and aggressive brain tumor, usually found in children, but rarely in adults, too. It originates in the brain's cerebellum, which is the control center for balance and coordination. It is a rapidly growing and spreading cancer, it is most detected after it has already spread to other areas of the brain and spinal cord, causing more damage and symptoms to present themselves. Signs and symptoms for MB will change from person to person, and based on the tumor size and location, but most commonly include headaches, nausea and dizziness, vomiting, loss of balance, and troubled vision, most symptoms being caused by the blockage of the cerebrospinal fluid (CSF) by the tumor, and often a shunt or drainage tube is placed to relieve the pressure felt by the patient. Like other cancers, there are several treatment options which can be tailored to each patient and their specific case, most

commonly, chemotherapy, radiation therapy, and surgery are used to treat and remove MB from the brain and spinal cord (if possible). In recent years, many new developments have revealed new treatments which include targeted therapies and immunotherapies, that have shown very promising results in clinical trials but will still undergo lengthy testing. The medulloblastoma cancer cells have many possible mutations which make treating this cancer especially challenging. It is with the hopes that the cancer can be removed without causing extensive damage to the human body, and without destroying the healthy tissues, especially those surrounding or near the tumor. With any cancer treatment, those risks are present, especially with the harsh chemicals used in chemotherapy, respectively. With motivated researchers and proper funding, there is no doubt that better, more targeted, and more precise treatments and therapies will emerge, and a cure for MB will eventually be developed.

In 2016, my twelve-year-old cousin Luke Fries was diagnosed with medulloblastoma and later passed away from it in 2019, at the age of fifteen. Since this devastating loss, I have made it a goal to learn more about this horrible disease and to understand what took away his life so young.

Medulloblastoma is a common type of brain tumor originating in the cerebellum, the part of the brain that controls balance and coordination. It is the most common type of malignant brain tumor occurring in children, which accounts for approximately 20% of all childhood brain tumors and is most common in children between the ages of 5-9 years old. Medulloblastoma can also occur within adults but is very rare, usually developing in the adolescent years and remaining dormant until later in life when detected and diagnosed. Medulloblastomas are rapidly growing tumors that can, and usually do spread to other parts of the brain and spinal cord

through cerebrospinal fluid (CSF). This is a type of primitive neuroectodermal tumor (PNET), which means that it develops from immature cells in the brain and spinal cord. PNETs are aggressive tumors that can grow and spread very quickly, most times before detection or diagnosis. Although the cause of medulloblastoma remains unknown, many researchers believe it may be due to a combination of genetic and environmental factors.

The symptoms related to MB vary depending on the location and size of the tumor, and whether it has spread before diagnosis. The most common symptoms include headache, nausea and vomiting, dizziness and loss of balance, double or blurred vision, mood and personality changes, and difficulty walking and talking. Some symptoms like headaches, nausea, and vomiting are due to the tumor blocking the flow of cerebrospinal fluid (CSF), causing extreme pressure in the patient's head. Usually, medulloblastoma is diagnosed by a combination of imaging tests, such as MRI, CT scan, and always a biopsy of the tumor tissue to confirm the presence of disease. Once the diagnosis has been officially made, the treatment options will depend also on the tumor location and size, and the patient's circumstances. Although the course of this disease hasn't been promising in later years, in most recent years the prognosis for patients has improved significantly, with an early diagnosis and aggressive treatment plan, up to 75% of children diagnosed with medulloblastoma can survive into adulthood.

The molecular genetics of medulloblastoma is very complex and has been the subject of intense research in recent years. This extensive research has led to the identification of four distinct molecular subgroups of MB. Sonic hedgehog (SHH)-activated, characterized by mutations in the genes that activate the Sonic hedgehog signaling pathway, such as PTCH1, SMO, and GLI2. WNT-activated, characterized by mutations in genes that activate the WNT signaling pathway, such as CTNNB1. Group 3, characterized by amplifications of the MYC and

MYCN genes. Lastly, Group 4, is characterized by a variety of genetic changes, including mutations in the TP53 and KMT2D genes. Each subgroup of this disease has its unique clinical features and prognosis. Like, SHH-activated medulloblastoma occurs predominately in infants, while WNT-activated medulloblastoma is predominately in older children. Group 3 medulloblastoma is associated with the worst prognosis of a 39% 10-year overall survival rate in infants and a 50% 10-year survival rate in children. Group 3 has the worst prognosis of all MB variants because it is stubborn to intensive multimodal therapy and therefore it is very difficult for treatments to even touch the tumor. Group 4 medulloblastoma is associated with an intermediate prognosis, it is nowhere near as difficult to treat as group 3, but still may display some stubbornness to treatment and therapies which could be even more taxing on the patient. Some of the most common, and specific molecular genetic changes present in medulloblastoma are PTCH1 mutations, SMO mutations, GLI2 mutations, CTNNB1 mutations, and MYC and MYCN amplifications. Amplification of these genes and mutations leads to increased gene expression of proteins, inhibiting the growth of the tumor. Although research continues for the molecular genetics of medulloblastoma, it is a slow and tedious process since it is the difference between life and death, this research is unveiling new and more effective treatments for this disease.

It is important to know and understand the molecular genetics of medulloblastoma in research because first, it can be used to classify the tumor to assist in developing a treatment plan specifically for its kind. Second, the molecular genetics of medulloblastoma can assist researchers in developing new and improved treatments for this disease, which would hopefully better the prognoses for each of the different subgroups. This research could include developing drugs to directly attack the WNT signaling pathway and the MYC and MYCN genes. MB is a

heterogeneous disease, with many different subtypes varying in molecular characteristics, clinical presentation, and prognosis, which all make the treatment for this disease rigorous and lengthy. A homogeneous tumor refers to the entirety of the tumor containing the same, or mostly the same genetic characteristics of the same tumor, or different tumors with the same genetic characteristics. A heterogeneous tumor refers to a bundle of different cells with different genotypes and phenotypes that may all present different biological behaviors within the same tumor.

As previously stated, the clinical signs and symptoms of medulloblastoma will vary depending on the location and size of the tumor, and if it has spread. The most common symptoms are related to increased intracranial pressure (ICP), which is due to the tumor blocking the flow of cerebrospinal fluid (CSF). The symptoms of ICP include headache – especially in the morning or after waking up, nausea and vomiting, dizziness, lethargy, blurred and doubled vision, papilledema (swelling of the optic nerve), difficulty walking or coordinating movements, seizures, and neck pain. If the MB tumor has spread into the spinal cord, additional symptoms such as weakness and numbness of the limbs, back and neck pain, difficulty walking, and difficulty controlling bladder or bowel movements, will likely present themselves. Regarding the tumor location, the patient may also have difficulty swallowing, speaking, or hearing. With CT imaging it has been found that 90% of tumors are hyperdense (which indicates a fresh clot formed by a vessel), 40-50% found cyst formation and necrosis (cell death) in common, calcification was apparent in 10-20% of cases, and enhancement is present in over 90% of cases and is usually prominent. With MRI imaging it has been found, hypointense (dark) or isointense (invisible) on T1-weighted images, hyperintense (bright) on T2-weighted images, diffusion restriction, and contrast enhancement. Other imaging findings include a mass arising from the

vermis (midline of the cerebellum), thinning of the fourth ventricle/ basal cisterns, and obstructive hydrocephalus (fluid on the brain). With MRI imaging, it is sometimes difficult to view the tumor depending on the type of image and the type of tumor that is present. With T1-weighted MRI images, the signal of fatty tissue is enhanced and suppresses the signal of the water, T2-weighted images enhance the signal of the water.

Medulloblastomas can be homogeneous and heterogeneous in appearance, found on imaging, depending on the presence of cysts, necrosis, or calcifications. They also vary in shape, size, and location, but usually have well-defined margins (useful in removal). Specific imaging features of medulloblastoma subtypes include WNT-activated medulloblastoma, often present as a midline mass with a homogeneous appearance found on an MRI. SHH-activated medulloblastoma typically has a more heterogeneous appearance on an MRI, with cysts and necrosis. Lastly, Group 3 medulloblastoma, has a more aggressive appearance on MRI, with infiltration into the surrounding brain tissues (not clear margins). There are hundreds if not thousands of imaging findings for medulloblastoma and they will vary from patient to patient. The histopathological diagnosis for medulloblastoma is based on three defining features, cellularity, medulloblastomas are highly cellular tumors with little to no stroma. Cell morphology, MB tumor cells are usually small and round or oval, with a dark-staining nucleus and minimal cytoplasm. Finally, mitotic activity, MBs are usually mitotic tumors with a high cell division rate, which almost always comes with cell abnormalities due to the rapid spreading and division.

Treatments for medulloblastoma vary, but are all very rigorous and lengthy, due to the aggressiveness of the tumor. Chemotherapy is a common cancer treatment that uses strong drugs to kill cancer cells, and it is one of the most effective cancer treatments. Chemotherapy has a

significant impact on immune-compromised cells because the drugs used are designed to kill rapidly dividing cells, which includes all cancer cells but sometimes, many types of immune cells as well. This will not only halt the cancer cell division but will also help prevent future relapses of the disease. Though chemotherapy is excellent in treating cancer cells, like anything else, it comes with its disadvantages. Chemotherapy can also cause damage to healthy cells, being that such strong drugs are used. The side effects on the healthy cells vary depending on the type of drug that is used and the dosage it is used in, but the side effects are usually temporary and will most times, revert to normal once treatments have ended. These side effects include myelosuppression – a decrease in the production of blood cells, including red blood cells, white blood cells, and platelets. This can lead to feelings of fatigue, anemia, infection bleeding, and hair loss. Chemotherapy drugs can damage the hair follicles, causing the patient to lose all hair on the body. Neuropathy, causes damage to the nerves, leading to numbness, tingling, and weakness of the limbs, the damage to the bone marrow where WBCs are produced can lead to neutropenia – a shortage of neutrophils. White blood cells are necessary for infection prevention and restoration. Reproductive toxicity causes irreversible damage to the reproductive organs leading to infertility among the individual. Cardiotoxicity, mouth sores, nausea and vomiting, and diarrhea. Though most of these side effects on healthy cells will be only temporary until after treatment has ended, some like neuropathy, reproductive toxicity, and cardiotoxicity, can be permanent.

The thymus is a gland that is a crucial part of T-cell development (a type of white blood cell that is necessary for fighting infection and cancer) and can be damaged in the mix of all the harsh drugs and treatments. During such harsh and lengthy treatment, inevitably, one's body wouldn't start to decline, but there are some preventative steps to help the process along, while

still nurturing your body. Like eating a nice, healthy, and nutrient-rich diet, even though one might lose their appetite, it is still important to nourish your body extra. Take vitamins and supplements to help replenish what has been lost or killed off with treatments. Medications can help prevent less life-threatening side effects but are only able to do so much in comparison to the harsh drugs that are being pumped into the body as treatment. Another very common and successful cancer treatment is radiation therapy.

Radiation therapy works by damaging the DNA of cancer cells, causing the cells to die immediately or to stop dividing and then eventually die. It can also damage the blood vessels which supply oxygen and nutrients to cancer cells, leading to their death. With any good and effective treatment comes its side effects. Side effects of radiation therapy on cancer cells include DNA damage, causing single-stranded or double-stranded breaks and crosslinks. If these damages don't repair themselves, it will lead to cell death. Apoptosis is programmed cell death triggered by DNA damage. Radiation can induce apoptosis in cancer cells by activating signaling pathways necessary for its activation. Necrosis is cell death caused by physical damage to the cell membrane or other components of the cell. Radiation induces necrosis by damaging the cell's DNA or by disrupting its blood supply. Lastly, senescence is a state of permanent cell cycle arrest. Radiation induces this by damaging the cell's DNA and signaling pathways. Senescent cancer cells are still alive, but are unable to grow or divide, preventing the spread or growth of the cancerous tumor. Additionally, radiation therapy can also damage healthy cells in the treatment area. This can cause minor and temporary side effects such as fatigue, skin irritation/rash, hair loss, and nausea. Radiation therapy is a safer and effective treatment for many cancer types and is usually the first treatment used since it is much less harsh on the body than some of the others. It is often used in combination with several other treatments like surgery and

chemotherapy, to improve the chances of resolution. Healthy cells damaged by radiation therapy can repair themselves after the treatment has ended. Doctors work consciously to minimize the damage to healthy cells during treatment. Several types of imaging tests are done to locate the tumor exactly, to target the tumor itself, and to plan treatment accordingly. Recently, newer technologies have been introduced and used such as intensity-modulated radiation therapy (IMRT) and proton therapy, which delivers a higher dose of radiation to the tumor while avoiding the healthy cells and tissue surrounding it. The benefits of radiation therapy greatly outweigh the risks, as it is a less harsh cancer treatment.

To reduce the damage to healthy cells during treatment, you can take extra care of your skin by cleansing and moisturizing more often, eating a healthy nutrient-rich diet, taking vitamins, and rest. The prognosis for medulloblastoma in recent years has improved significantly, with the 5-year survival rate now over 70% in children and over 50% in adults. The prognosis is best in children who are older when diagnosed and have tumors that are confined to the cerebellum and haven't spread, and who have not undergone a complete surgical resection. The prognosis is worse for children who are diagnosed younger or as infants because usually, they have tumors that have spread to another part of the brain and spinal cord or have a tumor that cannot be surgically removed. Prognosis-affecting factors include age at diagnosis, location of the tumor, extent of surgical resection, molecular subgroup, and treatment response. Surgery to remove medulloblastoma tumors is a very risky and complex procedure that is performed by a very skilled pediatric neurosurgeon. The goal of every removal surgery is to remove the entirety of the tumor (if possible) or as much as possible, with clean lines and margins to prevent the regrowth of the tumor from remaining cells left behind, and without damaging the healthy tissues

surrounding the tumor location. Most times a shunt will be placed before the removal of the tumor, to lessen the pressure inside the brain caused by the blockage of the CSF.

During surgery, the patient will undergo general anesthesia, and the neurosurgeon will make a cut and remove a piece of the skull to gain access to the brain. The tumor will be located and carefully cut out, a drainage tube (shunt) may also be temporarily placed, if it hasn't already, to reduce hydrocephalus. With any surgery comes risks and complications, the surgery to remove MB tumors is relatively safe, but some common risks include bleeding, infection, swelling of the brain, damage to nearby nerves or blood vessels, hydrocephalus (fluid buildup on the brain), and death.

The long-term outlook for children after MB removal surgery is particularly good, accompanied by a rigorous and successful treatment plan, most children will resume living normal lives. Supportive care is important for all patients with MB, regardless of their prognosis. Supportive care can help patients manage the side effects of treatments and surgeries, improve their quality of life, and emotionally support them through the changes they will face with such a disease. Some supportive care measures include pain management, nutritional support, physical and occupational therapy, speech therapy, and emotional support. For long-term survivors of medulloblastoma, supportive care is also necessary and beneficial. Survivors may experience long-term effects, or side effects years after treatment has ended such as cognitive impairment, hearing loss, and endocrine issues. With a supportive care team, MB survivors will be able to readjust to the world as the person they have now become, with the challenges they bring.

Targeted therapies are a newer type of treatment therapy for MB, that is designed to attack specific molecules or pathways involved in the growth and survival of MB cells. Targeted therapies are still under development, but some have shown very promising results in clinical

trials. Some of the most promising results from targeted therapies for MB include SMO inhibitors, WNT inhibitors, Aurora kinase inhibitors, and immunotherapy. Immunotherapy is one of the safest treatments as it helps the body's immune system fight cancer, immunotherapies like CAR T-cell therapy, have shown exceptional and promising results in recent clinical trials for MB, and have shown great promise in treating several types of cancers, but it is still relatively new in the treatment of medulloblastoma, the most common malignant brain tumor in children. Though targeted therapies are safer and are ideal, they are often used in combination with the traditional treatments of chemotherapy and radiation therapy. Targeted therapies can be more successful and long-term when used with other treatments.

Immunotherapy is still in the early stages of development for medulloblastoma, but the results of the early clinical trials have been encouraging and promising, and it offers a few advantages over traditional cancer treatments. It is more targeted and less likely to kill surrounding healthy tissue and cells. However, there are some disadvantages to immunotherapy for medulloblastoma treatment. First, the brain is an immune-privileged site, meaning it is difficult for the immune system to reach cancer cells in the brain. Second, the tumors are often heterogeneous, meaning they contain several different types of cancer cells, each with its mutations, making it more difficult to develop immunotherapies effective enough to fight against all of the different cancer cells of a given tumor. Immunotherapies are a new addition to precision medicine and despite the small challenges that have arisen, clinical trials have displayed that it has great potential to improve the prognosis and outcomes of the patient. Precision medicine is newly developed and is still in the early stages, but there are several clinical trials currently underway, that will test precision medicine approaches, their safety, and efficiency. Some of the most common targeted therapies are 'Targeted therapy against the Sonic

Hedgehog (SHH) pathway', 'Targeted therapy against the WNT/beta-catenin pathway', and immunotherapy. However, clinical trials have shown promising results for cancer treatment, especially medulloblastoma, and precision medicine has great potential to improve outcomes for patients with medulloblastoma by providing a more targeted and effective treatment, more research is needed to fully develop and prove precision medicine for medulloblastoma treatment.

Though there is no way to prevent medulloblastoma, or any cancer really, early detection and a good treatment plan will greatly improve the patient's prognosis. Researchers need to continue to uncover new treatments that may be safer and less taxing on the patient's body, so the chance of recovery can greatly increase. And though there have been several discoveries and developments with next-generation sequencing, liquid biopsies, and radionics, many of these discoveries are still in the early stages of clinical trials and will not become a prominent part of cancer treatment until they have fully proven themselves. With all the new technologies and recent developments in immunology, cancer research, and cell and molecular understandings, it is almost guaranteed that soon, the direction of treatment will be on track to help many more patients beat and survive MB.

Noticeably, medulloblastoma is the most common malignant and aggressive brain tumor found predominately in children, but it can also present itself in adults, rarely. This cancer is treated in the same way all others are, with chemotherapy, radiation therapy, and surgery, but none of that still seems to be enough, as there has not yet been a cure for this horrible disease. With no specific cause for this cancer, it comes with its challenges for developing specialized treatments and therapies. With cancer research and new technologies, it is confirmed that with new treatments and therapies on the rise, researchers and doctors will be able to better help the patients affected by such a disease. With the current 5-year survival rate for medulloblastoma

being 72.1%, it is obvious there is room for great improvement, and with funded research and motivated researchers, it is possible.

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