Meningiomas: A Biochemical, Genetic, and Pharmacological Review

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Abstract

A meningioma is a tumor originating in the meninges that cover the brain and spinal cord. While grade I meningiomas are easily treated with surgery, grade II and III tumors are much more difficult. They are also challenging to research due to limited number of subjects. This paper aims to look at the biochemical and genetic implications of meningiomas, the surgical approach and technological advances, as well as pharmacology information from the past, present, and future.

Introduction

Background

Based on data from 2012-2014, around 40 percent of people will be diagnosed with some form of cancer in their lifetimes (cancer.gov, seer.cancer.gov). These diagnoses will affect not only these people, but also everyone in their lives. If, somehow, someone manages to escape the emotional and physical stresses that come along with cancer, one cannot ignore the implications on the country as a whole; for example, the Agency for Healthcare research and Quality (AHRQ) gave a conservative estimate of $82 billion spent on direct medical costs in 2015 (meps.ahrq.gov). That figure is solely focused on cost of care and does not include all of the money going towards research, which for brain cancer was over 30 million in 2016. Many different treatments and therapies (including novel and repurposed drugs) are being researched for every type of cancer, but the rarer ones are more difficult due to the lack of subjects. There are many types of rare cancers, including grades II and III meningiomas.

It has been estimated that approximately 700,000 people have a primary brain tumor in the United States (braintumor.org). Of these, around 36 percent are meningiomas. A meningioma is a tumor originating in the meninges that cover the brain and spinal cord; the meninges consist of the dura mater, arachnoid, and pia mater. Most meningiomas occur in women aged 30-70, because of this it has been hypothesized that either estrogen or progesterone are involved with meningioma formation (abta.org, Caruso et al. 2015). The World Health Organization (WHO) has determined three classifications for meningiomas: I (typical), II (atypical), and III (anaplastic/malignant). Symptoms of grade I meningiomas include headaches, weakness in the arms and legs, vision problems, and mood changes (Bommakanti et al. 2016). As the grade increases, the severity and prognosis tend to get worse. However, the incidence goes down as the grade increases: about 85

percent of diagnosed meningiomas are grade I, around 10 percent are grade II, leaving approximately 5 percent at grade III. Those diagnosed with anaplastic meningiomas tend to have the worst prognoses since these are the most severe. All metastatic meningiomas are classified as grade III under the WHO classifications. A metastasis is a growth of cancer cells anywhere other than where they were initially formed (e.g. a tumor in the colon spreading to the liver). Only around five percent of all meningiomas are metastatic.

Case Study

Patient James LeBlanc, 47, visited his primary care doctor complaining of headaches, blurred vision, bouts of depression, and a recent onset of seizures. To rule out neurological problems, his doctor sent him to get an MRI. He was first diagnosed with a glioblastoma, an example shown in Figure 1c. Glioblastomas that are closer to the perimeter of the brain can be easily confused with meningiomas. He was then scheduled for surgery. Following surgery and further imaging, his diagnosis was changed to meningioma. After two more surgeries recurrence and metastasis occurred, showing that he had a grade III meningioma. At this point, another surgery was not an option. He went through rounds of chemotherapy including the drugs Dilantin, Temodar, and Interferon A. Dilantin had been taken continuously before the first surgery until

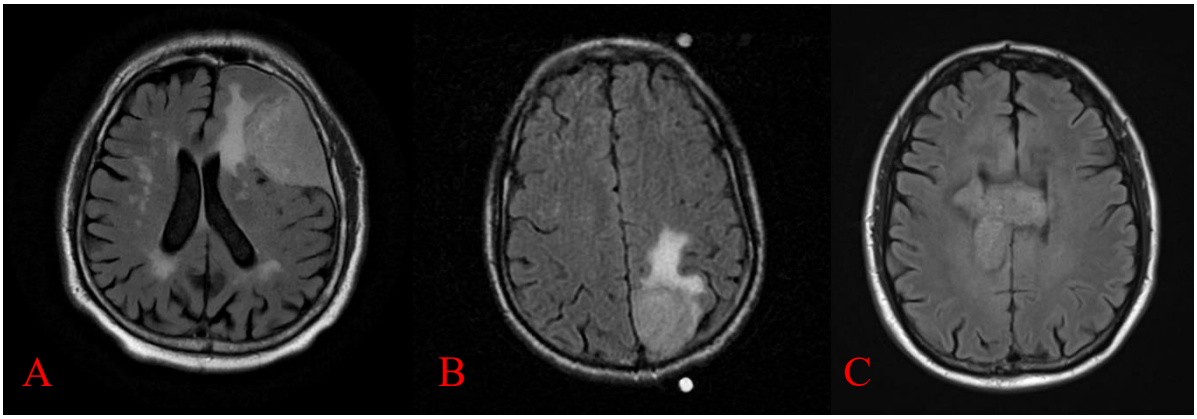

Figure 1. MRI scans of: A) typical meningioma, B) anaplastic meningioma, and C) glioblastoma. *Note that these are just one example of each type and does not represent all meningiomas or glioblastomas.

after the third and final surgery, was on Temodar for a short period after ceasing Dilantin, Interferon A was the final therapy initiated. (Case study from 1997-2000)

That was the story of my grandfather's battle with cancer, which likely mirrors many others. This paper is dedicated to him and everyone else who has lived through this devastating diagnosis. This paper will review biochemical and genetic aspects of meningiomas, as well as surgical/technological advances, current and proposed chemotherapy options, and the future of cancer treatment.

Biochemistry and Genetics

Transcription Basics

Transcription, in terms of genetics, is the process by which an RNA strand is formed using a DNA strand as a template. To begin transcription, the cell must first determine where the gene is and where to start transcribing. In order to do this, genes have a promoter region; this region acts as a starting point for RNA polymerase. In some cases, following the promoter region will be an operator. An operator essentially acts as an on/off switch for that gene; the gene can be 'turned off' (or not transcribed) if, for example, a repressor binds to the operator. The opposite is true if an activator were to bind to the operator. Transcriptional regulation is the front lines of regulating genes. Regulation may involve chromatin modulation, promoter escape, and transcription factors. While all genes use general transcription factors, some genes can have special ones designed to either speed up or slow down transcription of that gene. These are called activators and repressors, respectively. Repressors work by essentially acting as a roadblock for RNA polymerase. It will bind to the operator located downstream of the promoter and then RNA polymerase will not be able to continue transcription. Activators bind to an activator site located upstream of the promoter.

An activator will assist the general transcription factors that bind to the promoter so that they can start transcribing sooner.

Assuming transcription is not repressed, the RNA polymerase will proceed to bind to the promoter region and separate the two DNA strands at that site. Next, the RNA polymerase will move along the template strand of DNA, reading in the 3' to 5' direction. While it reads, it adds complementary nucleotides (A=U, C≡G) to the growing RNA chain. It is important to note that while the DNA is being read 3' to 5', the RNA is being built 5' to 3'. Eventually, the RNA polymerase will cross a sequence that signals the end of the gene. At this point the RNA polymerase will break off and the RNA will be prepared to leave the nucleus. RNA does not last very long in the cytoplasm by itself, so it undergoes some modification before it leaves. The RNA will get a 'cap' added at the 5' end and a poly-adenosine (poly-a) tail. These modifications allow mRNA to exit the nucleus without being degraded in the cytosol, where it then goes to be translated and becomes a protein. (Concepts of Genetics)

Cancer Cells and Metastasis

When viewed under a microscope, cancer cells look profoundly different than normal cells. Cancer cells will often appear irregularly shaped with one or multiple enlarged and course nucleus, giving it a somewhat threatening appearance. Meningioma cells, as shown in figure 2, typically surround each other in a spiral-like pattern and are often highly vascularized (Commins et al. 2007). Different types of cancer will ultimately be accompanied by various genetic mutations and disruptions; however, almost all cancer cells include an active form of telomerase. All cells contain telomerase for a while because it essential while healthy cells are still dividing. Telomerase extends the telomeres at the end of chromosome, eventually the telomere will become so short that the cell

knows it is time to die. In cancer cells, telomerase stays activated, extending the lifespan of these cells and giving them more time to multiply.

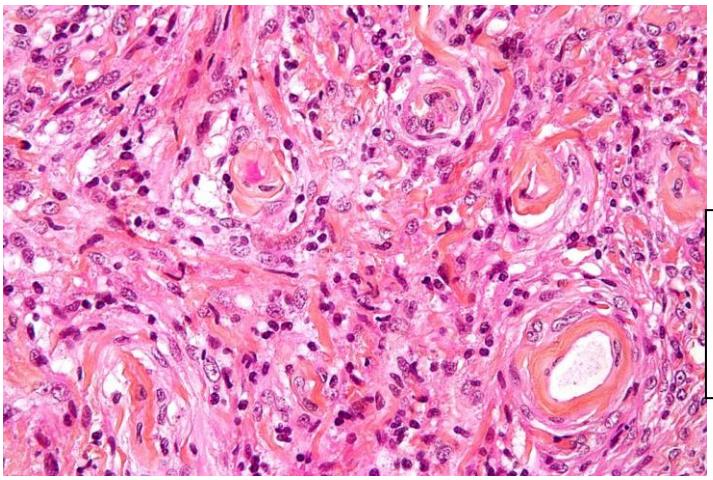

Figure 2. Shows a typical meningioma histology pattern. Upon growth they surround each other forming a whorling pattern.

A study done by Chang et al. (2013) and a case study by Och et al. (2016) examined the genetic malformations in meningioma cells. After performing a genetic analysis 19 meningiomas (spanning all grades) from different patients, Chang et al. were able to show different gene and chromosome abnormalities and compare them between each grade of tumor. They were able to show that grade II and III meningiomas showed a higher level of DNA mutation than grade I; they also revealed that nearly half of the samples tested showed changes on chromosome 22q (also supported by Och et al.). While the benign and atypical samples they tested shared many of the same mutations, malignant samples did not seem to resemble each other or the lower grades in terms of their genetic changes. The case study performed by Och et al. (2016) focused on a middle-aged man who presented with a grade II meningioma. After collecting samples and analyzing DNA over the course of his treatment, they found a loss of heterozygosity (LOH) at chromosomes 10, 14, and 22. They also noted an LOH at chromosome 1 which appeared around the time the tumor progressed to grade III.

As a tumor progresses to a higher grade, metastasis is more likely to take place. Metastasis occurs when tumor cells undergo epithelial-mesenchymal transition (EMT) and overcome anoikis. Anoikis is a type of apoptosis that occurs when a cell is no longer connected to its external matrix.

EMT occurs when a cell gets rid of its cadherins, which are membrane proteins that connect the cell with surrounding cells, and stop responding to the cell matrix. Usually, when an epithelial cell stops interacting with its cell matrix, it will die, but cancer cells have a mechanism to avoid this fate. This mechanism involves the regulation of various integrin proteins. The cells will 'escape' and become mesenchymal cells, allowing it to transfer to a new location. Once the cell arrives at a new tissue, it will reverse the process, implanting itself among new epithelial cells and begin multiplying.

MN1

The gene meningioma 1 (MN1) is a proto-oncogene, which means that it contributes to cancer pathology when mutated, and a transcriptional regulator. MN1 is also important for osteoblast formation and function. Without MN1, osteoblasts showed altered morphology and limited functionality (Zhang et al. 2009). MN1 is located at chromosome 22q12.1 and is 53,222 base pairs long. The MN1 protein consists of 1,320 amino acids (NCBI). It contains regions that are rich in proline and glutamine, which initially led researchers to believe it was related to transcriptional regulation. This was supported in a study done by Meester-Smoor et Al. (2007). They used a northern blot, a test used to detect explicit sequences of RNA, and a series of mutations to the promotor region of the IGFBP5 gene to determine that MN1 binds to a CACCC-rich segment of DNA near the promoter. While not all of the meningiomas tested were lacking MN1, the ones that did not contain MN1 were also missing IGFBP5. This supports the hypothesis that meningiomas can be caused by different events and the interaction between MN1 and IGFBP5 contributes to one of the causes.

A chromosomal mutation called translocation is responsible for some meningiomas losing the MN1 gene. Specifically, a translocation between chromosomes 4 and 22 can disrupt the MN1

gene and cause it to not be transcribed. Chromosome translocation describes the process by which either one chromosome gives genetic material to another or when two chromosomes exchange genetic material. These are termed nonreciprocal and reciprocal, respectively. The translocation involving MN1 is reciprocal and involves the trading of DNA between chromosomes 4 and 22 (remember that MN1 is found on 22). Another translocation that involves chromosome 22 leads to myeloid leukemia, another type of cancer which has also been shown to be linked to MN1 regulation (Chang et al. 2013, Meester-Smoor et al. 2007). While the exact mechanism of this translocation is unknown, it involves a breaking of the DNA strands and then a repair onto a heterologous chromosome.

When the (4:22) translocation occurs, chromosome 22 will break at the 5' exon of the MN1 gene. This causes MN1 to not be expressed, which then leads to IGFBP5 not being expressed.

IGFBP5

There are seven different insulin-like growth factor binding proteins that can either inhibit or enhance insulin like growth factors depending on where they are located. IGFBP5 is a protein-coding gene located at chromosome 2q35 consisting of 23,445 base pairs (NCBI). The protein it codes for goes by the same name and is around 270 amino acids long. This protein is responsible for mediating/inhibiting the activity of insulin-like growth factor 1 (IGF1) in connective tissues. As its name would suggest, IGF1 promotes growth in tissues and inhibits apoptosis. Therefore, without IGFBP5, IGF1 would proliferate cells rapidly and prevent cell death without any inhibition. Since meningioma cells are missing the MN1 gene and consequently the protein, this can cause major problems. When IGFBP5 is absent, IGF1 is allowed to freely induce proliferation and inhibit apoptosis (Chang et al. 2013, Meester-Smoor et al. 2007). This causes a rapid increase

of cells in a short amount of time. In the case of meningiomas, most of the tumors are benign and not necessarily cancerous; however, some of them will become malignant, invading nearby tissues.

HMGN5

HMGN5 stands for high mobility group nucleosome binding domain 5. This group of proteins is responsible for "various physiological process, including DNA repair, replication, transcription and recombination" (He et al. 2015). HMGN5 is located at Xq21.1 and is 88,242 base pairs long (NCBI). HMGN5 is overexpressed in many forms of cancer and He et al. were able to show a negative correlation between HMGN5 levels and prognosis (e.g. a higher amount of HMGN5 relates to a poor prognosis).

NF2

Neurofibromin 2 (NF2) is highly expressed during embryonic development. In adults NF2 can be found in Schwann cells, nerves, and the meninges. Its normal functions include managing cell shape and growth. This gene is located at 22q12.2 and is 95,045 base pairs long (NCBI). Mutations in this gene have been shown to contribute to the disease neurofibromatosis 2 and meningiomas. The study done by Zhang et al. (2014) was another genomic analysis, but this one focused solely on malignant meningiomas. Their observations supported the idea that mutations in NF2 (and MN1) can be involved in meningioma pathogenesis and malignancies.

Surgical Approach

Tumors typically form after a mutation in a cells genetic code promotes growth, stops cell death, or a combination of both. At the fundamental level, cancer treatments are designed to kill the proliferating cells or remove them completely. Some of the most common treatments include surgical removal, radiation therapy, and chemotherapy. For meningiomas, surgery is the primary

and most promising treatment. If the patients' tumor reoccurs or becomes malignant, it can make surgery more challenging and sometimes impossible (Och et al. 2016). Surgical removal of a tumor is simpler for those that are benign. While this option is still incredibly difficult for patients to undergo, the thought behind it is straightforward: remove the source of the growth and it will not grow anymore. The biggest downside of surgery, apart from the physical and emotional toll on the patient and their loved ones, is that even if a microscopic amount of the tumor remains it can re-establish growth. Radiation therapy focuses on using radiation to kill the cancerous cells by damaging the DNA found inside these cells to a point where replication (and therefore mitosis) is impossible.

Traversing the worlds of treatment in oncology can be problematic, especially when dealing with rarer forms (such as the grades II and III meningiomas). With this in mind, Sun et al. (2015) created a treatment algorithm for dealing with atypical and anaplastic meningiomas. Their algorithm included options consisting of surgery, radiation, adjuvant therapies, and joining clinical trials. This system can benefit many oncologists to help their patients with rare cancers that they may not have encountered before. It can also help the patient gain a sense of peace knowing that there are options going forward.

While the basis of surgery remains the same, developments in technology can help doctors be more precise, aid in planning the surgery, and reduce human error. Current developments in virtual and augmented reality are making it possible for neurosurgeons to practice difficult procedures and feel better prepared for their surgeries. As knowledge about artificial intelligence (AI) expands, many doctors and hospitals are looking to utilize this technology. One promising idea for use of AI in oncology is diagnosing tumors based on medical imaging. Some forms of

tumors can look very similar, so utilizing AI to process the minute details in a fraction of the time can help eliminate human error and enhance precision in diagnoses and planning.

Pharmacology: Drugs from Case

Phenytoin

The drug phenytoin is also known by the trade name Dilantin. This was one of the drugs given to the patient we met in the introduction. It is typically administered via intravenous (IV) or intramuscular (IM) injection and has a half-life of 10-15 hours. While the mechanism of action (MOA) of phenytoin is not fully understood, it is thought to be a voltage-gated sodium channel inhibitor (Walls et al. 2012).

Major side effects of phenytoin include: cardiovascular problems (V-fib), hepatic injury (acute hepatotoxicity, jaundice, hepatomegaly), hyperglycemia (inhibitory effect on insulin), and seizures[1]. The adverse side effect of ventricular fibrillation could support the idea that phenytoin is a sodium channel inhibitor as this side effect occurs with other sodium channel blockers (Morita et al. 2003).

Phenytoin is metabolized in the liver by CYP2C9 and CYP2C19; because of this it is highly susceptible to drug-drug interactions. When taken with a drug or substance that inhibits those CYPs, the phenytoin concentration in the body would stay higher for longer than it usually would, leading to possible complications and toxicity. Common drugs known to inhibit those CYPs are antidepressants, H2 antagonists[2], and antiepileptic drugs (AEDs)[3]. Conversely, when taken with

[1] Seizure side effects are typically associated with withdrawal from the drug as phenytoin is currently used as an anti-seizure medication.
[2] Used to reduce gastric acid secretions in the stomach
[3] Legge et al. 2018 found that taking an AED alongside a sodium channel blocker can produce a synergistic effect

something that promotes CYP activity, the phenytoin concentration may not be high enough to have a therapeutic effect. Common drugs that decrease phenytoin levels by activating CYPs are antiviral agents, diazepam, and different classes of AEDs.

This drug is currently used as an anti-seizure medication and is utilized in the oncology field following neurosurgeries to prevent seizures. While phenytoin is not utilized directly for chemotherapy, I included it due to its applications in the case and post-operative use.

Chemotherapy is the use of drugs to target cancer cells throughout the body. This is often the treatment of choice if the cancer is malignant since it can target cells throughout the body, whereas both surgery and radiation therapy are limited to only specific areas at one time.[4]

Temozolamide

The drug temozolamide is currently patented by Merck under the name Temodar. This drug can be administered orally or by IV and has a half-life of 1.8 hours. Absorption is affected by food presence in stomach (food presence will reduce rate and extent of absorption), so when taken orally it is advised to be taken on an empty stomach (this will also help prevent nausea). It has a volume of distribution (V_D) of approximately 30L and weakly binds to plasma proteins. Temozolamide has a low molecular weight and is lipid soluble giving it the capacity to cross the blood-brain barrier (a useful ability for drugs targeting the CNS) (Sarin 2010). CYPs play minor role in metabolism, so this drug does not have many drug-drug interactions.

[4] Some information for each drug came from RXlist.com which gives basic information available to both doctors and patients, such as side effects and major drug interactions. Citations for each drug used can be found in the Literature Cited pages.

Temozolamide can exhibit many side effects which vary depending on whether it is taken alongside radiotherapy (RT). Figure 3 shows the major adverse effects and the percentage of patients affected when taking temozolamide by itself or temozolamide plus RT.

Figure 3. The seven most common adverse reactions for patients taking temozolamide (with and without RT). Numbers are percentages of patients affected.

Adverse Reaction	**RT + Temozolamide**	**Temozolamide only**
Fatigue	54	61
Headache	19	23
Nausea	36	49
Alopecia	69	55
Rash	19	13
Vomiting	20	29
Convulsions	6	11

Temozolamide when taken is in its inactive form. However, once it enters the body it is rapidly hydrolyzed into its active form MTIC. MTIC is a cytotoxic agent which is very useful in the treatment of cancers. The cytotoxicity appears to come from its ability to methylate DNA at the O6 and N7 positions of guanine which can induce apoptosis. DNA methylation typically represses transcription It has been found that the efficacy of temozolamide can be improved by using Small interfering RNA or siRNA to inhibit the HMGN5 gene (Jing et al. 2015). SiRNA uses transposable elements, which are processed by the enzyme dicer, in order to stop transcription of certain genes. In the study done by Jing et al. it was shown that inhibiting the HMGN5 gene can enhance apoptosis; this can lead to an additive effect when in conjunction with temozolamide.

While temozolamide therapy exhibited disappointing results for the treatment of meningiomas, it is currently indicated in patients with glioblastoma and anaplastic astrocytoma (both of which are other types of brain tumors).

Interferon alfa-2b

This drug is patented by Merck under the brand name Intron A and is classified as an immunomodulatory therapy. It can be administered by IV, IM, subcutaneous (SC) injection, or intralesional injection; it has a half-life of 2-3 hours. Interferons are naturally produced by leukocytes within the body and show an anti-proliferative effect. This drug is modeled after a water-soluble protein that was originally obtained from the bacteria *E. coli*. The thought behind this drug is that by providing the body extra interferons, the anti-proliferatory effect will be amplified to combat tumor growth (Moazzam et al. 2013).

The most reported side effects include fever, headache, chills, and fatigue. These adverse effects get more severe as the dose increases. The most severe drug-drug interaction occurs with theophylline, which is a bronchodilator. Interferon alfa-2b can increase theophylline levels by 100 percent.

This drug is currently indicated for patients with meningiomas who are ineligible for surgery. It is also used in patients with leukemia, lymphoma, hepatitis c, and hepatitis b.

Pharmacology: Currently Used Chemotherapies

Hydroxyurea

The brand name of Hydroxyurea is Hydrea and it is administered orally. Hydroxyurea undergoes hepatic metabolism. If myelosuppression or cutaneous vasculitis occurs, the drug should be given at a lower dose or discontinued.

Hydroxyurea is an antineoplastic agent that is able to stop the cell cycle while it is in the s phase and induce apoptosis. It is able to do this by acting as a ribonucleotide reductase (RNR) inhibitor (Caruso et al. 2015, Moazzam et al. 2013, Sherman and Raizer 2012). RNR is an enzyme that converts ribonucleotides into their deoxyribonucleotide equivalent which are needed in order to synthesize and repair DNA. Therefore, by inhibiting RNR the cells are unable to continue surviving (Kolberg et al. 2004).

Hydroxyurea is currently used as a chemotherapeutic agent for meningiomas and chronic myeloid leukemia.

Octreotide Acetate

Also known by the brand name Sandostatin LAR, this drug is a somatostatin analog. Studies on meningiomas have shown a high frequency of somatostatin receptor expression (Caruso et al. 2015, Sherman and Raizer 2012). It has a half-life of 1.7 hours and a V_D of 13.6 L. Octreotide acetate (OA) is given monthly as an intragluteal depot injection. OA has been shown to inhibit glucagon and insulin release; blood glucose levels should be monitored and diabetic patients may have to adjust other medications they are on. Somatostatin analogs can inhibit CYP3A4 activity, therefore drugs that are metabolized by this CYP should be used with caution.

The inhibitory hormone somatostatin naturally occurs in the body; its functions include preventing cell proliferation and suppressing the release of gastrointestinal hormones along with inhibiting other hormone secretions throughout the body. OA performs the same actions as

somatostatin, however it is more potent. Cancer patients who receive OA have exhibited adverse reactions such as abdominal pain, nausea, and gallbladder abnormalities (e.g. jaundice and gallstones).

OA is indicated for patients with meningiomas and other CNS tumors as well as patients with acromegaly.

Pharmacology: Proposed Repurposed Drugs[5] and Clinical Trials

Proposed repurposed drugs

Growing frustrated with the outcomes of previous and current chemotherapies, Zador et al. (2018) set out to find drugs that would counteract signature meningioma gene expressions. They sampled and analyzed gene expression from 47 meningioma samples as well as 4 samples from healthy meninges. Once they found the disease-specific gene expressions, they compared it to the gene expressions correlating with known drugs. The drugs that countered the disease-specific expression were then further examined. Of those, the top 3 candidates were verteporfin, emetine, and phenoxybenzamine.

Verteporfin

Currently, verteporfin (trade name: visudyne) is used to treat patients with macular degeneration, myopia, or ocular histoplasmosis. It has a half-life of 5-6 hours. The drug in administered via IV along with light from a diode laser. Verteporfin is metabolized by the liver, but CYPs seem to play a minor role.

[5] For proposed repurposed drugs, a majority of the information came from RXlist as well as the paper by Zador, King, and Gelfman 2018.

Once injected, verteporfin enters the plasma and is transported by lipoproteins. Verteporfin enters the body in its inactive form and is activated by the light from a diode laser. Once activated, it produces oxygen based free radicals that damages the endothelium. This leads to the release of leukotrienes and thromboxane which can result in platelet aggregation and vasoconstriction.

Zador et al. found that verteporfin was able to interfere with a YAP pathway and an EGFR pathway present in meningiomas. The YAP1 protein was found to induce cell proliferation and was shown to be overexpressed in meningiomas. By interfering with this pathway, verteporfin can hinder proliferation and meningioma progression. They were also able to show that after treatment with verteporfin, radiation therapy on meningiomas was more successful. EGFR is a growth factor receptor which, as the name suggests, stimulates growth when activated. Since EGFR is expressed in 50-80 percent of meningiomas, verteporfins' interference of it makes it a promising chemotherapy candidate.

Emetine

Emetine is a naturally occurring substance used to treat amoebiasis and is also used to induce emesis. Emetine has been shown to be an inhibitor of translation which subdues protein synthesis. Zador et al.'s analyses found that Emetine inhibits some anti-apoptotic proteins present in tumors as well as CYP3A4. Furthermore, it was shown to reduce glioblastoma tumor growth in mouse models, showing that it could also be used for meningiomas.

Phenoxybenzamine

This drug also goes by the trade name Dibenzyline and is currently indicated in patients diagnosed with a pheochromocytoma (a tumor located on the adrenal glands). This drug is administered orally with approximately 25 percent being absorbed in the active form.

Phenoxybenzamine may interact with alpha and beta adrenergic receptor agonists and amplify their effects. Phenoxybenzamine acts as a non-selective adrenergic alpha-receptor antagonist which can cause vasodilation and hypotension.

This drug was shown to be an inhibitor of glioblastoma cell viability in vivo. Like verteporfin, Zador et al. found phenoxybenzamine to inhibit EGFR pathways. It also inhibits a protein called calmodulin which has been found in meningiomas, however its effects on meningioma tumor progression is unknown. Generally, calmodulin is a calcium binding protein which enhances cell proliferation and metastasis in other tumors.

Current clinical trials

Imatinib mesylite

This drug is also known as Gleevec. It is taken orally and should be taken with a meal. This drug has been used to treat many forms of leukemia and gastrointestinal tumors; it also recently completed phase II of its clinical trial for treatment of recurrent meningiomas. Phase II found that almost 30 percent of their patients showed no tumor progression over 6 months while taking this drug with an average survival time of 17 months. This drug should not be taken with CYP3A4 inducers (including dexamethasone[6], phenytoin, and carbamezapine[7]). The most common side effects while taking imatinib mesylite include edema, congestive heart failure, hepatotoxicity and hypothyroidism.

Imatinib mesylite functions as a protein-tyrosine kinase inhibitor that enhances apoptosis and hinders cell proliferation. Hatva et al.'s (1995) study examined the relationships between

[6] An anti-inflammatory agent
[7] An anti-convulsant, sometimes prescribed off-label for bipolar disorder

tyrosine kinases and brain tumors/metastases. They did this through analysis of various tumor samples (including glioblastomas, meningiomas, and astrocytomas) and control tissues from healthy brains. While only one control sample showed expression of one specific receptor tyrosine kinase, almost every sample of every brain tumor tested showed at least one form of receptor tyrosine kinase. This makes it a promising candidate for clinical trials, not only for meningiomas, but for other brain tumors as well.

Nivolumab

Nivolumab also goes by the brand name Opdivo and is administered via IV injection. This drug is currently used in patients with many forms of cancer, including: melanoma, lung cancer, renal cell carcinoma, lymphoma, colorectal cancer, and hepatocellular carcinoma. In other forms of tumors, the efficacy of nivolumab has been shown to increase with the addition of the drug ipilimumab. A phase II clinical trial testing the efficacy of nivolumab on recurrent grade II or III meningiomas is currently recruiting patients.

Nivolumab in a monoclonal antibody that is found in humans. It can block the interactions between programmed cell death protein 1 (PD1, commonly found on T-cells) and its complementary ligands. When PD1 is bound to its ligand it inhibits the t-cells from killing any other cells (including tumor cells). By blocking this interaction nivolumab increases the likelihood that the body's t-cells will kill off the cancer cells.

Gene Therapy

Gene therapy is a relatively new form of treatment that is still being heavily researched. The idea was first conceptualized in 1972, but research didn't begin until 1980, and the first 'success' was in 1993. This success was the first time that a permanent genetic change occurred

by novel DNA introduced. Very few successes have been achieved in terms of treatments for diseases. Many of the first studies used viruses as vectors to bring the desired DNA into the system. This proved to be dangerous, so other methods have been and are being tested, including naked DNA and clustered regularly interspaced short palindrome repeats (CRISPR). CRISPR-cas9 has proven to be the most promising mechanism thus far. CRISPR-cas9 was modeled after a protective mechanism found in bacteria to defend them from invading viruses. When a bacterium is infiltrated by viral DNA, the bacteria will cut off some of the invading DNA and create what is called a CRISPR array. This array works similarly to a human memory B cell in that if the virus infects again, the CRISPR array will remember it from the DNA it contains and be able to get rid of it more quickly (Hsu et al. 2014). This process does require some modification for use in editing DNA. There is a piece of guide RNA which escorts the cas9 protein to the region of DNA to be modified. The cas9 then acts as DNA scissors and creates a double strand break at the point it was led to. The intended gene can then be integrated into the damaged DNA (Reiss et al. 2014). The development of CRISPR-cas9 opens doors in the fields of food engineering, fuel and material engineering, and medicine.

A review paper put together by Luigi Naldini (2015) shared some clinical trials that showed encouraging results and safe outcomes. However, for gene therapy to become integrated into modern medicine, much research is still needed as well as ways to ensure patient safety. That being said, gene therapy would open up a whole new world of personalized medical treatments, being able to replace mutated genes, knock out mutations, and be able to cater a treatment for the patient instead of for the disease. For example, in the case of MN1 deficient meningiomas, the MN1 gene could be added back in to compensate for the mutation. This treatment is difficult because of the very delicate homeostatic balance in cells. While an MN1 deficiency can lead to various diseases

(meningiomas, myeloid leukemia, and cleft palates), having too much could inhibit connective tissue growth which is needed for development (Zhang et al. 2009). Once it is fully developed, gene therapy has the potential to change the world of medicine. However, it could also introduce an interesting dichotomy between doctors who differ in opinions about the morality of this novel treatment.

In order to fully explore the idea of gene therapy, one must also consider the possible negative consequences. These include negative outcomes that have already happened during research trials and the potential effect on socioeconomic separation already prevalent throughout the world. In terms of results, there have been relatively few success cases. There are many clinical trials surrounding it, so it may be able to be redeemed. It has been highly controversial which can make progression difficult. If gene therapy becomes a main form of treatment, the cost alone will further isolate the poor in terms of healthcare. There are also some ethical issues involving its potential to be used cosmetically and the role it could play in changing the human gene pool. Focusing solely on America as a nation, taxes would inevitably increase due to the additional funding for medical care and research.

Final Thoughts

The realm of science is constantly expanding as new discoveries are made. It is extremely fascinating how advances in one field can inspire others and lead to cooperative growth as a scientific community. I loved learning the ways that biochemistry, genetics, and pharmacology could fit together in examining and solving a specific problem. While so much progress has been made in the medical and pharmacology disciplines, there is still so much room to grow especially in oncology and genetic diseases. It will be interesting to see if anything comes to fruition

regarding Zador et al.'s proposed repurposed drugs. I also can't wait to see where the technology and advances surrounding gene therapy take the medical world.

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