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An Interdisciplinary Review of the Qualities of Glioblastoma Multiforme

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SUMMARY

Using a cross-disciplinary approach, this review aims to cover the defining features of Glioblastoma Multiforme (GBM), an aggressive and highly lethal brain tumour. GBM is the most commonly diagnosed malignant brain tumour that has one of the lowest survival rates of any cancer today. In this review, a discussion of the epidemiology, prevention measures, detection methods, and treatment methods are provided to present a holistic analysis of the current and future medical approaches to GBM. Although the genetic risk factors of GBM cannot be prevented, certain lifestyle-related changes can potentially decrease one's chances of developing GBM. Additionally, through its many properties, CT scans offer a detailed account of the condition of various areas of the brain. Furthermore, a fractionation schedule of 2.21 Gy was calculated to maximize cancer tissue death and minimize normal cell death in potential treatments. These findings illustrate the importance of understanding GBM and how modern-day strategies can shape future attempts to combat malignant growth.

ABSTRACT

Brain cancer, despite being one of the rarest forms of cancer, is one of the most substantially impactful cancers known to humankind. In this review, a comprehensive analysis of the multifaceted nature of brain cancer is conducted, with a particular focus placed on Glioblastoma Multiforme (GBM). Epidemiology, prevention measures, treatment techniques, and determinants of susceptibility are investigated to gain a deeper understanding of GBM. Additionally, the biophysical concepts used in Computed Tomography (CT) scanning for tumour detection are explored. Radiation therapy as a treatment modality for GBM is examined using Intensity Modulated Radiation Therapy (IMRT). Furthermore, the mechanism of action of Temozolomide, the prevailing chemotherapeutic drug used to hinder GBM growth by methylating target DNA sites, was also analyzed. Additionally, a cell survival curve outlining a traditional fractionation schedule of 2.21 Gy installments was created to effectively model a conventional radiation treatment plan. As a result, we are able to gauge the efficacy of such radiation treatments. In summation, we present a broad synopsis of the current strategies, insight, and approaches used to detect, image, and treat the malignant growth of GBM.

Keywords: Brain cancer, glioblastoma multiforme, CT scans, chemotherapy, radiation therapy

INTRODUCTION

Cancer belongs to the family of diseases typified by the development and uncontrollable growth of abnormal cells with the ability to destroy surrounding body tissue.[1] Brain cancer is defined as the uncontrollable growth of abnormal tissue in the brain and is divided into two main categories based on the tumour's area of origin: primary and metastatic.[2] Primary brain tumours may originate in the brain itself, or in nearby tissue such as the meninges, cranial nerves, or pituitary or pineal glands.[3] This review is centered around GBM, a primary brain tumour. GBM is a fast-growing glioma, a general term used to describe primary brain tumours.[5] Metastatic brain tumours are more common, and arise from cancer developing elsewhere in the body and metastasizing to the brain.[3,4] Recent studies indicate that GBM develops from astrocytes, which are star-shaped glial cells that support neuronal function, and also carry various neural stem cell-like properties.[2,7] The most frequent location of origin for GBM is the cerebral hemispheres of the brain, with a smaller percentage of GBMs occurring in the cerebellum, brainstem or spinal cord.[5] GBM is an invasive intracranial tumour that commonly spreads through direct infiltration and extension into adjacent brain tissue. The metastatic spread of GBM outside of the central nervous system (CNS) is rare.[6] Additional research into GBM reveals incidence is slightly higher in men than women, and in Caucasians relative to other ethnicities.[7]

1.1 EPIDEMIOLOGY

Although brain tumours and other such malignancies of the CNS are rare, their mortality remains disproportionate to their global incidence.[8] In Canada, a GBM diagnosis is a grave predicament, and only 4% of diagnosed Canadians aged 45-54 retain a five-year relative survival.[9] Despite survival rates varying worldwide, a strong correlation exists between lower Human Development Index (HDI) and increased incidence and mortality of brain cancers.[10] Increased monitoring of risk factors and access to earlier detection and treatment plans are instrumental to controlling brain cancer in higher HDI level nations.[10]

As of 2015, GBM is the most common malignant tumour in Canada, and the third-most reported tumour at an average of 5691 cases per year.[11] For Canadian men, GBM was the most commonly diagnosed brain tumour, with an average annual incidence of 562 cases.[11] As seen in Figure 1, three major nations, England, United States, and Canada, each saw visible GBM incidences increase from 1995 to 2015. In this 20-year span, Canada witnessed a crude percent increase of 26.4% in age-standardized GBM incidence rates, and by 2015, Canada held a rate of 4.50.[12]

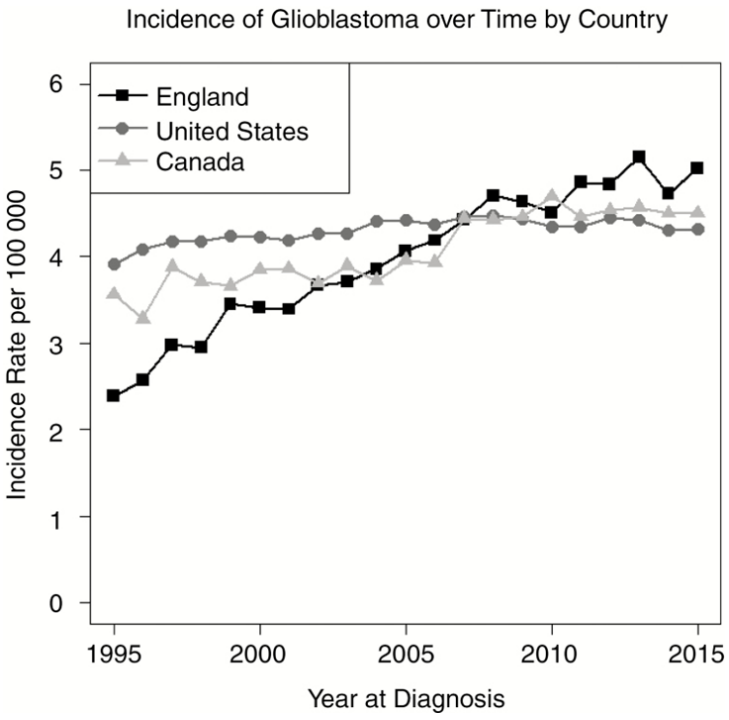

Figure 1. Graphical representation of the incidence rate of GBM as a function of time in years from 1995 to 2015. The graph shows an increase in GBM incidence for all three of these developed nations. Canada saw a 26% increase in GBM incidence in this 20-year span of data collection.[12]

Despite these findings, it is widely accepted that the attribution of any environmental factor as a conclusive explanation for historical GBM incidence rates is premature.[12] Philips et al. postulates that the frequent exposure to ionizing radiation from CT imaging in nations such as England and Canada may be contributing to rising GBM incidence within the past 25 years.[13] Risk factors will be expanded upon in the following section. In spite of the recent advancements in treatment and diagnosis of GBM, long-term survival rates remain stagnant, as prognosis and risk factors of GBM are rudimentary.[14]

2.1 RISK FACTORS, GENETIC SUSCEPTIBILITY, AND PREVENTION

Many insights into the driving factors behind oncogenic transformation have been uncovered over the past few decades. In essence, cancer is a genetic ailment that is caused by alterations to gene structure and expression. However, many external factors contribute to its diagnosis. Numerous risk factors have been associated with the development of brain cancers, however, most brain tumors are not linked to any known predisposing risk factors and have no obvious cause.[15] This section details both lifestyle-related and non-modifiable risk factors associated with GBM.

2.1.1 Behavioural and Lifestyle-Related Risk Factors

Despite the vast research into the etiology of GBM, most of its causes remain unknown.[16] A plethora of lifestyle-related risk factors such as alcohol consumption and smoking, along with other considerations such as infectious agents, and blood transfusion have been explored. Regardless of all this research, the evidence for their role as risk factors for GBM is inconclusive.[16] Although statistical correlation to GBM incidence is low, three variables are worthy of further investigation: dietary levels of glucose, the intensity of carbon tetrachloride exposure, and radiation exposure.

Bao et al. investigated the effects of hyperglycemia on the growth of GBM cells and discovered high glucose promoted proliferation and inhibited GBM cell apoptosis through enhancement of growth factor receptors and chemoattractant production. This team concluded that type 2 diabetes mellitus is an independent risk factor for GBM cell growth.[17] Additionally, Nelson et al. determined the consequences of occupations with medium or high exposure to carbon tetrachloride, such as firemen or machinists, were independently associated with GBM development. Carbon tetrachloride exposure was not linked to the development of any other cancer.[16] Finally, a systematic review conducted posits that moderate-to-high-dose ionizing ra-

diation exposure is positively associated with glioma, meningioma, and various other CNS-related tumour risks, however, the precise nature of this relationship at lower-level exposures is not well characterized.[18] The direct relation between these factors and GBM development remains unclear, thus further research is required to elucidate the degree of their significance.

2.1.2 Genetic Susceptibility

Genetic susceptibility refers to the possibility of developing a particular disease due to changes to genetic composition. Unlike the lifestyle factors discussed, genetic risk factors are not avoidable, as they are often pre-existing. Genetic factors for GBM often come in the form of mutations, which can lead to the overexpression of genes that support oncogenic transformation. There are numerous genes and cancer predisposition syndromes that may influence the risk of GBM. If these factors can be identified, therapeutic treatments can be designed to target these specific genes.

Epidermal growth factor receptor (EGFR) proteins are receptor tyrosine kinases that control signal pathways responsible for the growth, reproduction, motion, and survival of tumour cells.[19] The EGFR gene mediates the production of these proteins, and therefore influencing the susceptibility to develop GBM. Nearly 50% of glioma patients have amplified EGFR expression, indicating that the overexpression and/or variance of EGFR is likely correlated with brain tumours.[20] Tumours that contain EGFR amplifications also may also consist of numerous EGFR mutations such as EGFRvIII, a common mutation found in 30% of GBMs.[19] EGFRvIII-mutated cells are resistant to EGFR inhibitors, providing a greater chance of survival and a more malignant phenotype.[19,20]

In recent studies, the overexpression of Advillin (AVIL) has shown links to GBM and tumorigenesis. Xie et al. demonstrated that AVIL overexpression is found in the majority of GBMs, suggesting that GBM cells depend on excess AVIL for survival.[21] AVIL interacts with F-actin, an essential protein involved in various cellular functions, such as cell motility and transcription regulation, that is vital for the motion and signaling pathways of GBM cells.[21,22] As silencing AVIL would reduce GBM growth, it acts as a good therapeutic target.[21]

GBMs are associated with numerous familial cancer predisposition syndromes. Li-Fraumeni syndrome results from mutations in mitotic checkpoint genes, such as TP53 and CHEK2, and Turcot's syndrome is the result of mutations in various genes required for DNA repair.[23] Due to the high amount of gene mutations, these two syndromes increase the risk of GBM development through uncontrolled cell growth and replication.[23]

When considering the risk factors of GBM, it is also important to consider family history. Brain tumours may cluster within families due to shared environmental exposures and gene inheritance.[23] Identifying a family history of GBM would allow patients to seek testing early. Furthermore, since immune system effectiveness decreases with aging, individuals older than 65 have a greater risk of GBM development.[24]

Considering these factors, there are currently no verified methods to prevent GBM. Although exposure to these factors may increase the likeliness of developing GBM, further research is required to illuminate a stronger correlation to GBM.

3.1 OVERVIEW OF CURRENT DETECTION METHODS

Cancer detection is a crucial and challenging aspect of cancer treatment. There are various neurological symptoms a GBM patient may experience, such as headaches, vomiting, or speech difficulty that imply the need for further testing.[25] Magnetic Resonance Imaging (MRI) and CT scans provide valuable diagnostic imaging for GBM.[26,27] Early detection, however, is challenging. As of 2019, there are no standard diagnostic methods for early-stage GBM.[28] Researchers have attempted to use MRI technology to study early stages of tumorigenesis. However, the challenge with this approach is that it is difficult to distinguish the early-stage tumour from non-cancerous disorders from the images generated.[26,27] As a result of late detection, GBM is difficult to treat, resulting in a poor prognosis with a median survival time of 14.6 months.[28] In general, new detection technologies must be developed to improve GBM detection.

3.1.1 Imaging Technique

GBM is an aggressive brain cancer that is difficult to treat, so its early diagnosis is crucial to a patient's long-term health. Patients that display neurological symptoms will first be administered a physical exam consisting of an assortment of neurological function tests, including reflex, coordination, and alertness evaluations.[29] Subsequently, GBM is diagnosed with a series of imaging tests, generally MRI and CT scans.[30] To aid in diagnosis, a biopsy may be performed to extract a sample of abnormal cells for testing in a pathology laboratory.[29]

Head MRI is an advantageous evaluation technique because it possesses higher contrast of available soft tissue, higher sensitivity for brain abnormalities, and depicts anatomy in greater detail.[31] Compared to a 62.35% sensitivity of CT screening, MRI is 78.82%

sensitive.[32] CT scans, however, are faster and less expensive than MRI scans, making CT screening the preferred option.[31]

3.1.2 Computed Tomography Scans

A CT scanner is a large, donut-shaped machine with a short tunnel in the center (Figure 2).[33] The patient lies on a narrow examination table that slides within the tunnel while image processing occurs in a separate control room.[33] CT screening employs X-ray images taken from various angles around the body to provide a detailed image of the brain.[34] If a potential abnormality is identified, a follow-up exam will be scheduled for further evaluation. The doctor will examine any changes in the abnormality over time and determine whether the prescribed treatment is causing the abnormality to change or remain stable.[35]

Figure 2. Model of a standard CT scanner. The patient will lie on the patient couch (patient table), which is led through the tunnel opening, or the X-ray tube gantry. The imaging and data collection occur within the opening, as this is where the X-ray tubes are located. During imaging, these tubes move around the patient to create an image.[36]

As several electronic X-ray detectors and X-ray beams rotate around the patient, the CT scanner measures the amount of radiation absorbed throughout the body. A computer produces a large volume of data to create individual two-dimensional images or grouped three-dimensional cross-sectional images of the body.[33] CT scans use X-rays with energies ranging from 20 to 150 keV, as the tissue density in the body greatly varies.[37] The drawbacks of CT scanning have been widely studied; the financial burden patients experience when taking multiple CT scans can be debilitating.[38] Furthermore, the radiation a patient receives may lead to further cancer complications in the future. However, if GBM is diagnosed at an early stage, this disadvantage may be considered admissible. Additionally, due to the comprehensive nature of a CT scan, its results may suggest against further testing, allowing a potentially false report to prevent definitive testing.

3.1.2 Physics of CT Scans

By design, the purpose of a CT image of the brain is to provide a detailed image of brain structures for insight into potential disease or injury. There are three dominant physical processes responsible for the interaction of an X-ray signal with brain matter: photoelectric absorption, pair production, and Compton scattering.[39] For clinical imaging, photoelectric effect is the primary mechanism, as CT scans occur at lower energies. The photoelectric effect describes the complete absorption of a photon when it interacts with an atomic inner electron.[39,40] As a photon's energy exceeds the binding energy of an electron, all the photon's energy is transferred to the electron, emitting the electron from the atom, a process illustrated in Figure 3.[40]

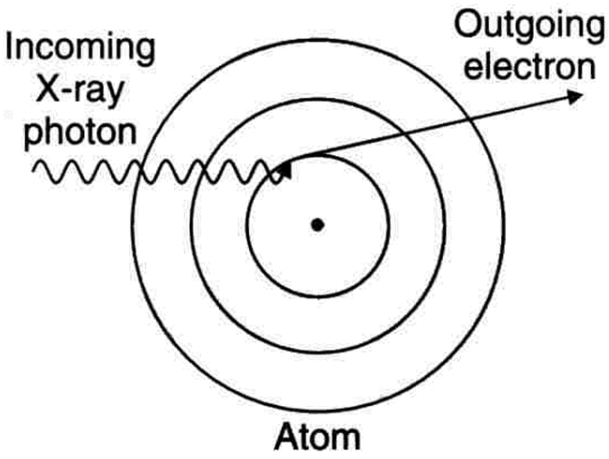

Figure 3. Pictorial representation of the photoelectric effect during a CT scan. The incoming X-ray photon is absorbed and causes an electron to be emitted, resulting in the attenuation of the incoming X-ray beam. The emitted electron, due to having a very short pathway, will also be absorbed very quickly.[41]

Due to the photoelectric effect, upon tissue interaction, X-ray signals either scatter or are completely absorbed.[40] This demonstrates the concept of photon attenuation; the gradual energy loss of a beam as it passes through matter, a phenomenon calculated using Beer's Law in equation (1)[39]:

$$\textit{Equation 1}: \qquad I = I_0^{[-\mu_i x_i]}$$

Here, the transmitted intensity, I, can be calculated by raising the incident intensity of an X-ray to the power

of μ_i, the linear attenuation coefficient multiplied by x_i, the length of the X-ray path through the matter.[39]

As the tube rotates and irradiates the head of the patient, detectors continue to compute the transmitted intensity, converting these values into an electrical signal and relaying these signals to a computer.[42] Once these values are digitized—a process by which each signal is assigned a whole number—a digital matrix of pixels is created. Thereafter, each pixel is converted to Hounsfield Units (HU) to create a two-dimensional image. Alternatively, several two-dimensional images can be combined to create a three-dimensional image. The conversion is calculated through equation (2)[43]:

$$\textit{Equation 2}: \quad HU = 1000 \times (\mu_{tissue} - \mu_{water}) / \mu_{water}$$

Upon conversion to HU, a visible map of low-density tissue (darker, blacker colours), organs (shades of grey) and higher-density structures (brighter, whiter) tissues is created.[44] As humans can only perceive a limited number of gray shades, the full range of density values is traditionally not displayed during imaging. Instead, brain tissue will be highlighted by devoting visible gray shades to a reduced portion of the full density, a process called "windowing".[44]

Contrast material may be applied orally, intravenously, or rectally to allow a radiologist to differentiate normal and abnormal conditions.[45] For head CT scans, iodine-based contrast materials are injected intravenously to reduce the amount of scattered radiation. Therefore, the resolution of brain tissue temporarily containing iodine-based compounds has a slightly emphasized appearance on CT images.

CT imaging is a powerful tool for GBM; its ability to rapidly create detailed images and monitor the efficacy of treatment makes it the primary choice for GBM diagnosis.[46] Comparatively, the cost and time required for MRIs make it a less ideal imaging method, constituting CT as the leading imaging technique.

4.1 RADIATION THERAPY

4.1.1 Overview of Radiation Therapy

There are various treatment approaches available for GBM patients. Due to the aggressive nature of GBM and its dangerous location within the CNS, it is challenging to remove the entire tumour surgically. Radiation therapy uses high-energy beams to kill cancerous cells and prevent further replication. GBM patients typically receive radiotherapy daily for several weeks to allow fractionation, a method that will be expanded upon below.[47] In comparison to other treatments, radiotherapy is a local treatment, meaning it affects a limited portion of the body. As a result, radiotherapy has few side effects.

External Beam Radiation Therapy (EBRT) is the process of delivering high-energy photons from an external source such as a linear accelerator.[48] Although there are various methods of radiotherapy delivery, this review focuses on Intensity Modulated Radiation Therapy (IMRT) due to its efficiency in targeting cancerous cells while protecting surrounding healthy tissue.[48]

4.1.2 Intensity Modulated Radiation Therapy

IMRT is a type of three-dimensional conformal radiation therapy (3D-CRT) that utilizes CT imaging.[48] 3D-CRT treatment planning involves the beam's eye view which finds an optimal beam direction to deliver radiation to the tumour that will protect critical nearby organs.[48] A linear accelerator is used to generate energy beams for IMRT, such as photons or X-rays. The intensity of the beams is regulated based on the arrangement of the tumour with relation to surrounding organs. In IMRT, the intensity of radiation beams passing through organs at risk (OARs) is reduced, whereas the beams that pass through the target are increased.[48,49] The intensity and angle of the beams are controlled using multileaf collimators, devices that consist of many individual leaves.[48,49] These leaves can each be moved about the radiation pathway to block the beams from reaching specific destinations.[48] As a result, the radiation dose is directed to the target without interfering with OARs.

X-rays and gamma rays are preferred for radiotherapy due to their high energy levels, which are required for the Compton Effect and ionization.[50] The Compton Effect is a mechanism by which photons react with matter, such as tissue, and explains radiotherapeutic interactions in the body. When a high-energy photon such as an X-ray is directed towards tissue, it collides and releases a weakly-bounded electron. While some energy is utilized by the electron, the remaining energy is conserved by releasing a lower-energy photon.[50] This photon interacts with other electrons and the process continues further to ionize the targeted tissue.[50] The photoelectric effect is less common in radiotherapy as low-energy photons are required. The process differs from the Compton Effect as the interaction between photons and tissue only. releases electrons, not lower-energy photons.[50]

Ionization can damage cells directly through DNA double-strand breakage.[47] DNA breakage is prominent during mitosis. However, cells spend 95% of their life in interphase, thus spending less than 5% of their time in mitosis.[51] This issue is resolved through fractionation, the process of delivering small radiation doses daily in order to affect the greatest number of cells in

mitosis. As of 2020, 60 Gy with standard fractionation (2 Gy/day) is the standard radiotherapeutic approach to GBM.[50] Fractionation is effective as normal cells repair much quicker than cancerous cells. As a result, damage towards healthy cells is minimal.

Ionization through the Compton Effect damages cancerous cells indirectly through the production of reactive oxygen species (ROS), such as superoxide anions, hydroxyl radicals, hydrogen peroxide, singlet oxygen, and hypochlorous acid.[50] These molecules are reactive due to an unpaired electron in their valence shell. Although ROS are necessary for the regulation of physiological functions, excess levels cause oxidative stress and damage to cellular components, thus provoking double-strand breakage and apoptosis.[52]

In general, IMRT is an efficient treatment method for GBM patients that efficiently kills cancerous cells through ionization and the production of ROS. Although radiotherapy can be used solely, quality of life is improved alongside chemotherapy or surgery.

4.1.3 Cell Survival Curve and Radiation Treatment Schedule

To effectively model optimal radiation doses and the varying survival ratios of cancerous and normal tissue cells, a cell survival curve was formed. From experimental research, we identified α/β ratios of three and ten for normal and cancer tissue respectively for GBM radiation treatment. Figure 4 demonstrates the relationship between cell reproductivity and increased radiation dose during treatment.

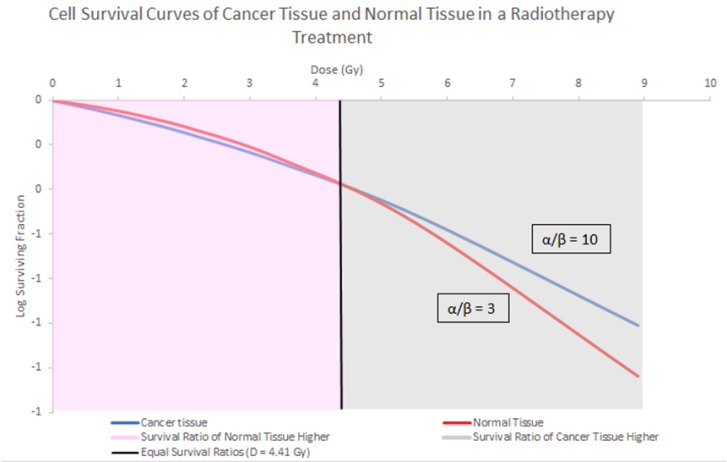

Figure 4. Graphical representation of a cell survival curve of both normal and cancer tissue within a patient undergoing radiation therapy for GBM. α/β ratios of three and ten were used for normal and cancer tissue respectively, and the dose at which there are equal survival ratios is 4.41 Gy (black line). The purple portion of the graph represents the dose at which the survival ratio for normal tissue is greater than cancer tissue. The gray portion of the graph represents the dose at which the survival ratio for cancer tissue is greater than normal tissue. The initial population for both tissue samples was 1000 cells.[53,54]

To calculate the number of surviving cells analogous to the dose administered, equation (3) was used. However, for graphing practicality, equation (4), the natural logarithm of equation (3), was utilized.

Equation 3:

$$Number\ of\ Surviving\ Cells = S = 1000(e)^{-\alpha D - \beta D^2}$$

Equation 4:

$$Log\ Surviving\ Fraction = ln(S) = -\alpha D - \beta D^2$$

Figure 4 also depicts an intersection at a dose of 4.41 Gy, indicating an equal survival ratio of cancer and normal tissue. Consequently, we observe that at radiation doses greater than 4.41 Gy, more cancerous tissue survives, while at doses lower than 4.41 Gy, more normal tissue survives. As a result, it is imperative to find the optimal dose at which the difference between normal and cancerous tissue is greatest. To determine the optimal dose, the derivative of the difference between the equations for cancer and normal tissue is set to zero (Equation 5). This enables us to calculate the dose at which the maximum number of cancer cells are eliminated while sustaining normal cells.

Equation 5:

$$f(D) = (-0.06D - 0.006D^2) - (-0.035D - \frac{7}{600}D^2)$$

$$f'(D) = 0 = -0.025 + \frac{17}{1500}D$$

$$Optimal\ Dose = D = 2.21\ Gy$$

After calculating an optimal dose of 2.21 Gy, a function illustrating the fractionation treatment of a typical GBM patient can be drawn. Figure 5 demonstrates the importance in determining the optimal radiation levels to curtail normal cell death and maximize cancer cell death. Furthermore, Figure 5 exhibits the increasing difference between cancer and normal cell populations at a radiation dose of 2.21 Gy.

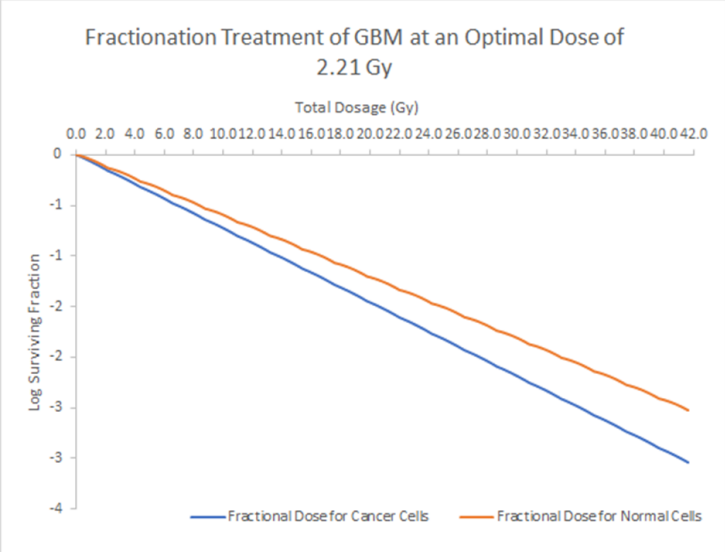

Figure 5. Graphical representation of a Fractionation Treatment for GBM at an Optimal Dose of 2.21 Gy. The curve illustrates the exact amount of radiation that can be administered to maximize cancer cell death while simultaneously minimizing normal cell death. As the dose applied increases, the disparity between cancer cell and normal cell populations grows greater. The initial population for both tissue samples was 1000 cells.[53,54]

5.1 CHEMOTHERAPY

Chemotherapy is a drug-based treatment option for cancer patients. Chemicals are delivered to the tumour via oral ingestion or injection to inhibit cancer cell proliferation. Unlike radiation, which can be targeted to specific tissues, chemotherapy is a systematic treatment that affects most of the body, resulting in numerous side effects. Temozolomide (TMZ) ($C_6H_6N_6O_2$) is the standard chemotherapeutic agent for GBM that was first approved in 1999.[55,56] TMZ is sold under various brand names, such as Temodar® and Temodal®. The chemical properties of TMZ, in particular, its lipophilicity, allow it to reach the brain and treat GBM efficiently.[57] TMZ can also be used to treat other gliomas, such as anaplastic astrocytoma.

5.1.1 Method of Action of Temozolomide

TMZ is delivered orally through the use of pills. Since TMZ is small and has a relatively low molecular weight of 194 g/mol, it is quickly absorbed in the digestive tract where it can enter the bloodstream.[58] Consequently, the molecule is 100% bioavailable after absorption.[58] In addition to surgical resection and 60 Gy of radiation in 30 fractions, standard care for GBM patients includes 75 mg/m²/day of TMZ for six weeks.[59] Following initial treatment, patients typically undergo six maintenance cycles of TMZ to prevent GBM return. Patients receive 150-200 mg/m²/day for the first five days of a 28-day cycle.[59]

Brain tumour treatment using chemotherapy is challenging due to the blood-brain barrier. The blood-brain barrier is an important structure that regulates the movement of ions and molecules between the blood and the brain.[60] The strict regulation protects the brain from toxins, pathogens, and unfortunately, chemotherapeutic agents. TMZ is ideal for GBM treatment due to its lipophilicity. Unlike other therapeutic agents, TMZ can easily penetrate the blood-brain barrier, quickly absorb into the cerebrospinal fluid, and distribute appropriately.[57] This property allows TMZ to reach brain tumours in sufficient concentrations.[57]

TMZ is an alkylating agent prodrug, which stops the transcription of DNA into RNA through the substitution of alkyl groups for hydrogen atoms. This process halts the cell cycle by preventing protein synthesis and provokes cell death.[56] More specifically, TMZ is categorized as a triazene, a molecule that metabolizes to form intermediates that alkylate biological molecules.[61] TMZ undergoes hydrolysis to form active monomethyl triazeno imidazole dacarbazine (MTIC) at blood pH, thus no metabolic activation is required.[57] The MTIC intermediate breaks apart to form methyl diazonium ions that react with nucleophilic sites on DNA. The interaction between the methylated DNA and DNA repair pathways provokes cell death.[62]

DNA methylation occurs at specific nucleophilic sites, most of which are at guanine-N7, guanine-O6, and adenine-N7.[57,62] However, the mutations at guanine-N7 and adenine-N3 are fixed through base excision repair and are TMZ resistant.[56,57] Of the sites listed, TMZ is the most effective at guanine-O6. In order for TMZ to be effective, mispairing of DNA bases must take place. The methylation of O6-guanine results in mispairing with thymine during DNA replication. The mismatch pair is recognized by DNA mismatch repair (MMR) proteins, causing cycles of thymine removal and reinsertion.[63] This process breaks DNA strands, resulting in the activation of DNA damage response mechanisms. As a result, cell cycles halt and apoptosis occurs.[63] However, the methylation of O6-guanine can be repaired by a specific enzyme, O6-methylguanine-DNA methyltransferase (MGMT), once again resulting in TMZ resistance.[62,63] Therefore, in order to ensure apoptosis by TMZ, tumours must have low amounts of MGMT and sufficient levels of MMR.[62] Figure 6 illustrates the pathway by which TMZ is effective.

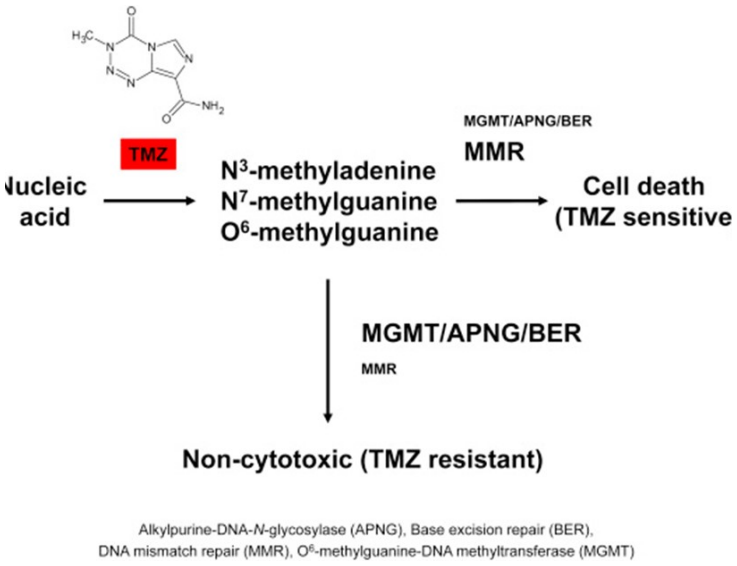

Figure 6. The mechanism of action of TMZ. TMZ adds methyl groups to three specific locations, N3-adenine, N7-guanine, and O6-guanine. The modifications can be reversed by MGMT and BER, leading to TMZ resistance. Mismatch repair proteins must be present in sufficient amounts to cause cell death.[56]

Since chemotherapy is a systematic treatment, it affects a majority of the body. Since healthy cells are also susceptible to TMZ action, TMZ induces numerous side effects. Bruising, headaches, constipation, and fatigue are side effects greater than 10% of patients experience.[64] Although chemotherapy is effective in prolonging patient life, more research is required to reduce the side effects of TMZ.

CONCLUSION

GBM is an aggressive brain cancer that continues to threaten public health. In this review, we analyze the potential risk factors, diagnoses, and treatment approaches to GBM. The role of CT scanning as an imaging technology in GBM diagnosis was explored while outlining the challenges neurologists face when diagnosing brain cancer. Due to the lack of early-detection methods, GBM has a low prognosis with a 14.6 month median survival.[28] Although GBM is challenging to cure, there are various treatment modalities used to improve patient comfort and life expectancy. IMRT damages cancerous cells both directly and indirectly through ionization, whereas TMZ passes through the blood-brain barrier to methylate target DNA sites. Both treatments result in cancerous cell death. In order to increase GBM survival rate, more cancer research regarding GBM detection and treatment is required. As technology advances, researchers will continue to uncover new information about GBM and potentially discover new methods to treat or cure this form of cancer.

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APPENDIX

Information was gathered through McMaster library keyword searches and online searches. Through a compilation of findings from journal articles, academic books, credible organizations, and academic reports, we were able to synthesize and report on our understandings. A focus was placed on finding peer-reviewed literature from the last ten years to ensure our reporting was accurate and suitable for today's environment.

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