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Recent Advances in the Treatment of Diverse Patient Populations with Brain Cancer

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ABSTRACT

Brain cancer, the leading cause of cancer-related deaths in children and young adults, presents unique challenges due to the complexity of the disease and the limitations of current treatment options. Targeted therapies, immunotherapies, and combination therapy approaches have emerged as innovative strategies to address the heterogeneity of brain tumors and enhance the effectiveness of treatment. Novel drug delivery systems and advancements in immunotherapy have shown remarkable potential in overcoming the blood-brain barrier and targeting specific molecular pathways involved in tumor growth. By individualizing treatment approaches and leveraging the patient's own immune system, recent research has illustrated remarkable progress in halting tumor progression and even consistently reducing tumor volume for the first time. This review will discuss the challenges historically faced for treatment development, current treatment options for patients, and where the field is headed with new treatment options. Despite the challenges ahead, continued focus on research and development in this field holds the promise of revolutionizing brain cancer treatment and improving outcomes for diverse patient populations.

Keywords: Brain cancer, Targeted therapies, Immunotherapy, Blood-brain barrier, Combination therapy

Introduction

Brain cancer is a complex and challenging disease that can affect individuals of all ages, with distinct differences in clinical presentation and prognosis between primary and metastatic forms. Primary brain tumors originate within the brain tissue itself, while metastatic brain tumors spread to the brain from other parts of the body. The anatomy of the human brain is shown in Figure 1. According to recent statistics, brain cancer is the leading cause of cancer-related deaths in children and young adults under the age of 20.¹ The prognosis for children and young adults with brain cancer varies depending on the type and stage of the tumor, with survival rates ranging from a few months to several years.¹

Cancer in children and adolescents and young adults (AYA) is a unique subset of cancer that encompasses individuals from birth spanning up to 25 years old. Brain cancer is one of the most common types of cancer in this age group, with gliomas and medulloblastomas being among the most prevalent.² The incidence of brain cancer in youth has been on the rise in recent years, highlighting the need for improved treatment strategies and outcomes. This group often remains underserved due to the lack of understanding and tumor heterogeneity presented with these cases in

a developing brain.² Understanding the specific challenges and characteristics of brain cancer in children and AYA patients is crucial for developing targeted and effective therapies to incorporate all the patient populations involved.

Diagnosing and treating brain cancers have been particularly challenging due to the complexity of the disease and the lack of specific symptoms in the early stages.²⁻⁴ The average survival rates for different types of brain cancer, such as glioblastoma multiforme, are notoriously low at an average of 9 months post-diagnosis.⁵ Brain tumors post-treatment also have a high likelihood of treatment failure and recurrence even after aggressive treatment regimens.⁶ The invasive nature of brain tumors and their proximity to critical brain structures make complete surgical resection difficult, leading to limited treatment options and poor outcomes for many patients.⁶

Despite the historical challenges in treating brain cancer, recent advances in targeted therapies and novel technologies offer new hope for all patient populations. While targeted therapy for brain cancer or brain metastasis remains limited, ongoing research and clinical trials are exploring innovative approaches to personalize treatment. In this review, the latest advances in the treatment of brain cancers for diverse patient populations will be highlighted to illustrate promising results and the potential for improved outcomes compared to previous decades of limited success in the field.

Challenges Presented by the Blood-Brain Barrier

The blood-brain barrier (BBB) is a highly specialized protective barrier that separates the circulating blood from the brain tissue, maintaining a stable and controlled environment for the brain. Composed of tightly packed endothelial cells, the BBB regulates the passage of substances in and out of the brain, allowing essential nutrients to enter while blocking potentially harmful molecules.⁷ This selective permeability is crucial for protecting the brain from fluctuations in the bloodstream and maintaining homeostasis within the central nervous system.

In normal physiological conditions, the BBB plays a key role in transporting essential nutrients, such as glucose and amino acids, into the brain while removing waste products and maintaining the proper balance of ions and water.^{8,9} This selective transport mechanism ensures that the brain receives the necessary resources for optimal function while preventing the entry of harmful substances that could disrupt its delicate balance. However, when it comes to drug delivery, the BBB presents a significant challenge due

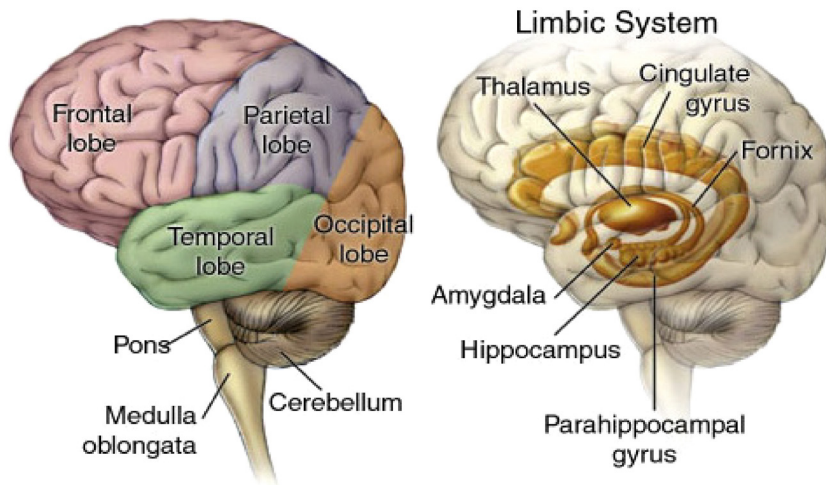


Fig 1 | Anatomy of the human brain

to its ability to restrict the passage of many therapeutic agents into the brain. Efflux transporters actively pump out and remove drugs that manage to cross the BBB, further limiting their effectiveness in reaching therapeutic concentrations within the brain.^{7,10}

Only a select few drugs or compounds with specific characteristics are able to permeate the BBB and exert their desired effects within the brain. Lipophilic molecules, small in size and possessing certain transport mechanisms, are more likely to cross the BBB successfully.¹¹ Efforts are underway to develop innovative drug delivery systems and formulations that can enhance the permeability of the BBB and target specific regions of the brain. By utilizing techniques such as nanoparticles, liposomes, and receptor-mediated transport, researchers aim to overcome the challenges posed by the BBB and improve the delivery of therapeutic agents to the brain. Despite these obstacles, recent advancements in drug delivery technology have shown promise in overcoming the limitations of the BBB, offering new opportunities for targeted and effective treatment of neurological disorders and diseases.

Historical Prognosis of Brain Cancer

The human brain remains one of the most intricate and enigmatic organs in the human body, with its complexity and intrinsic properties still largely unexplored. The root cause of brain tumors in all patient populations remains largely unknown, which adds another element of difficulty by hindering the front-end prevention of the disease as well. Despite advancements in technology and medical research, the brain continues to be a mystery in many aspects. It is astonishing to think that humans, at points in history, have discovered more of the ocean depths or the surface of the moon than the organ between our two ears. Even with the most modernized equipment and technology available today, misdiagnosis and errors in detecting brain conditions and diseases, such as tumors, still occur at

alarming rates that often lead to adverse events.¹² This highlights the challenges faced in accurately diagnosing and treating brain tumors due to the delicate nature of the brain and the limitations of current medical technologies.

Current technologies for detecting and diagnosing brain tumors include magnetic resonance imaging (MRI), computed tomography scans, and positron emission tomography scans.¹³ These imaging techniques help visualize the brain and detect abnormalities, such as tumors shown in Figure 2. However, the sensitivity of this equipment varies, and detecting small amounts of mutated cells in the brain below current detectable limits can be challenging. Even a minuscule number of cancerous cells in the brain can have significant consequences due to the vital functions of the brain. This emphasizes the importance of early detection and accurate diagnosis of brain tumors to improve treatment outcomes and patient prognosis.

Over the past few decades, significant progress has been made in the detection and treatment of brain tumors. Advances in imaging technology, surgical techniques, and targeted therapies have revolutionized the management of brain cancer.¹⁴ Detection limits have improved, allowing for earlier diagnosis and intervention. Brain cancer diagnosis is now more reliable with the development of molecular markers and genetic testing.¹⁵ Treatment options have also expanded, with a focus on personalized medicine and targeted therapies tailored to individual patients. The historical prognosis and treatment of brain tumors have significantly evolved, offering renewed optimism for patients, yet it still remains far from desirable outcomes.

Current Treatment Options for Brain Cancer

Historically, the treatment of brain tumors has been challenging, with limited success in eradicating or slowing tumor progression. Common approaches have included the use of FDA-approved chemotherapy drugs such as temozolomide, carmustine, procarbazine, vincristine, and lomustine, which work by targeting rapidly dividing cancer cells.¹⁶ Procarbazine, lomustine, and vincristine are commonly used in combination for the treatment of brain tumors, particularly glioblastoma multiforme. This regimen works by targeting the different aspects of tumor growth and proliferation, enhancing the overall effectiveness of the treatment.¹⁷ In conjunction with chemotherapy, corticosteroids are often prescribed to reduce swelling and edema around the tumor, while seizure medications help manage symptoms associated with brain tumors.¹⁸ While these drugs have shown some efficacy in certain cases, their non-specific nature often leads to significant side effects and limited effectiveness in targeting the tumor cells specifically.

Adjuvant therapies such as radiation therapy may also be used to complement the primary treatment and improve outcomes for patients with brain tumors. Gamma knife radiotherapy combines the radiation therapy with surgical excision techniques to carefully

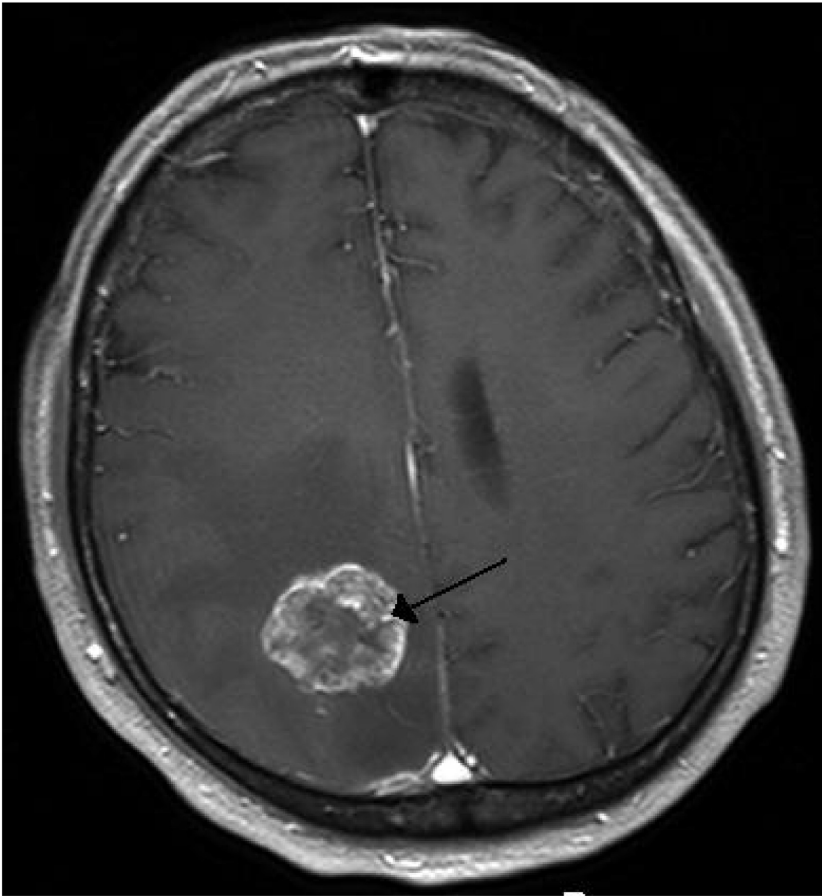


Fig 2 | MRI of a metastatic brain tumor

and precisely remove cancerous tissues from the healthy cells in the brain.¹⁹ Clinical presentation and tumor location dictate the adjuvant therapy options that may be utilized to provide the patient with optimal outcomes.

In addition to chemotherapy and radiation, targeted therapies such as bevacizumab and erlotinib have been approved for certain types of brain tumors, aiming to inhibit specific molecular pathways involved in tumor growth. Drugs like erlotinib and bevacizumab work by inhibiting specific enzymes or receptors that are overexpressed or mutated in cancer cells while sparing healthy brain tissues. Bevacizumab is used in combination with chemotherapy for aggressive brain tumors because it operates by inhibiting the growth of new blood vessels in order to restrict vascularization around the tumor and cut its essential lifeline of nutrients in order to starve the cancer.²⁰ Erlotinib works on non-small cell lung cancer (NSCLC) that has metastasized to the brain. Erlotinib targets an epidermal growth factor receptor that is often overexpressed in NSCLC to prevent the cancer from proliferating uncontrollably in a subset of cells that often remains resistance to other lines of treatment.²¹

These targeted therapies may be used alone or in combination with chemotherapy and radiation to enhance their effectiveness and minimize side effects.

Despite the progress made in recent years, a new group of medications known as immunotherapies holds the greatest promise in the treatment of brain tumors.

Immunotherapy: The Latest Drug Development and Clinical Trials in Brain Cancer

Immunotherapy has revolutionized the treatment of various types of cancers by harnessing the power of the immune system to target and destroy cancer cells. However, applying immunotherapy to brain tumors has been particularly challenging due to the BBB and the immunosuppressive microenvironment within the brain.²²

Several immunotherapies are currently FDA-approved or in late-stage clinical trials for the treatment of brain tumors, showing promising results in halting tumor growth and even inducing significant tumor shrinkage. Examples include checkpoint inhibitors like pembrolizumab and nivolumab. These two drugs are monoclonal antibodies that work by targeting the overexpressed programmed death ligand 1 (PD-L1). The structure of an antibody is shown in Figure 3. These drugs prevent the binding of PD-L1 from a patient's immune cell, allowing the immune cells to remain active and kill the cancer cells.²³ A targeted therapy mentioned above that doubles as an immunotherapy called bevacizumab is also a monoclonal antibody, but this treatment targets the molecular pathway of vascular endothelial growth factor to prevent the growth of blood vessels around the tumor. Even tumor-specific vaccine development is underway with drugs such as dendritic cell vaccine (DCVax-L) that operate by training the patient's own cells to recognize and remove the brain cancer cells, given the biomarker instructions they have been provided with by the vaccine.^{24,25}

Immunotherapy has even spanned to the historically underserved cancer population of pediatric patients by developing an anti-cancer therapeutic called dinutuximab.

Dinutuximab is a monoclonal antibody targeting an overexpressed cancer marker in children with neuroblastoma called GD2 (a disialoganglioside) that has shown recent efficacy in prolonging survival and time of relapse in high-risk pediatric patients.²⁶ The success of these clinical trials highlights the potential of immunotherapy to significantly improve outcomes for patients with brain tumors by utilizing their own immune system to join in the fight against cancer.

In recent years, several drugs and therapies involving the immune system have shown remarkable promise in preclinical studies for the treatment of brain tumors. For instance, immune checkpoint inhibitors targeting novel immune checkpoints like LAG-3 and TIM-3 have demonstrated efficacy in preclinical models of glioblastoma.²⁷

One stand-alone treatment option that has shown the most striking results in the history of brain cancer treatment, in preclinical and clinical trials, is called adoptive cell therapy. Adoptive cell therapy takes a patient's own immune cells and extracts them from

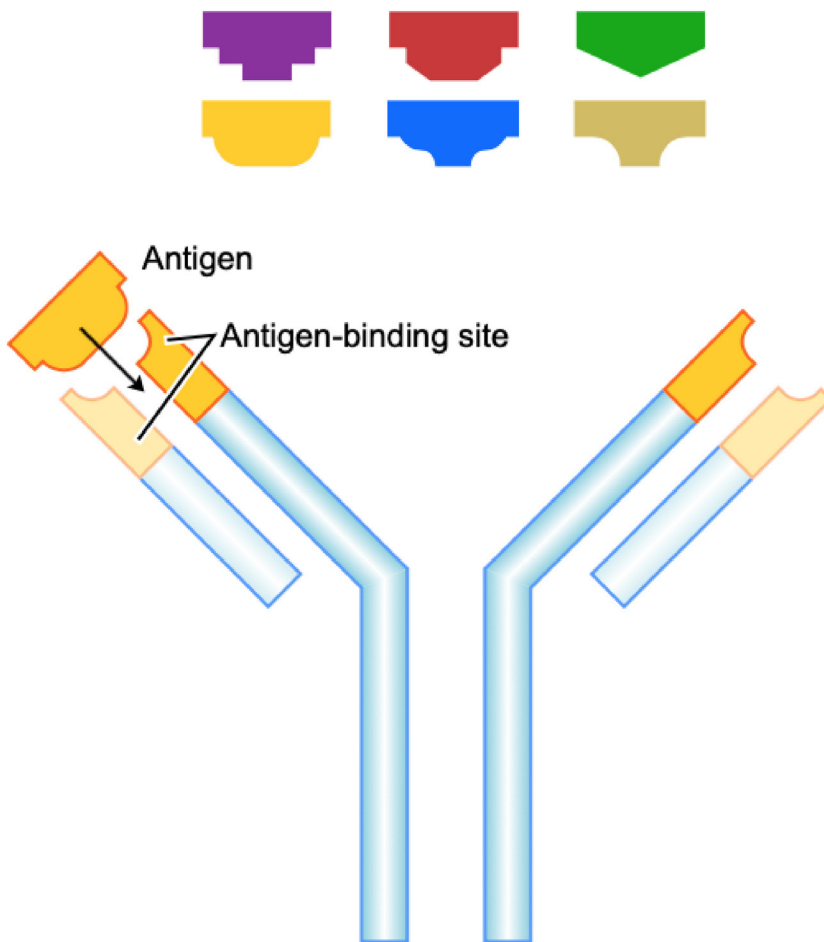


Fig 3 | Antibody structure

the body to perform molecular engineering that augments and equips the cells with the necessary means to recognize and kill the cancer in the body when placed back in the patient. One promising approach is chimeric antigen receptor T-cell (CAR-T) therapy, which involves genetically modifying a patient's T-cells to recognize and attack patient-specific tumor cells. Groundbreaking findings in an interim report of a stage I clinical trial illustrated the reduction of several patients' aggressive glioblastomas with the specialized CAR-T therapy received.²⁸ These are among the most remarkable results ever seen in the treatment of brain cancers. CAR-T therapy has shown great potential in treating brain tumors by overcoming the limitations of traditional treatments and enhancing the immune response specifically against cancer cells in the brain. This study will continue to be followed for long-term outcomes and additional treatments.

Additionally, adoptive cell therapies using tumor-infiltrating lymphocytes and natural killer cells have shown potent anti-tumor activity in preclinical studies, paving the way for their translation into clinical trials for patients with late-stage and aggressive brain tumors as well.²⁹

The current landscape of immunotherapies in clinical trials, along with the promising candidates in pre-

clinical development, holds the potential to surpass all the past FDA-approved therapies for brain cancer. By individualizing treatment approaches and leveraging the patient's own immune system as a biological weapon against challenging brain cancers, these innovative immunotherapies offer a personalized and targeted strategy that could revolutionize the field of brain cancer treatment.

Targeting Only Part of a Whole: The Need for Combination Therapy

Despite advancements in cancer treatment, drug resistance remains a significant challenge leading to treatment failure and tumor recurrence, often due to the inherent heterogeneity of tumors. To address this issue, combining a comprehensive array of broad-spectrum drugs, targeted therapies, and immunotherapies may offer a promising solution to enhance treatment efficacy and improve patient outcomes. By leveraging the strengths of different treatment modalities, combination therapy has the potential to overcome resistance mechanisms, target multiple pathways, and create a synergistic effect that can effectively combat the complexity of cancer.

A potential combination therapy approach could involve administering a cocktail of chemotherapy agents, targeted drugs, and immunotherapies tailored to the specific characteristics of the patient's tumor.³⁰ This personalized treatment strategy aims not only to eradicate cancer cells but also to minimize the development of resistance by attacking the tumor from multiple angles. Additionally, incorporating drug regimens or drug holidays into the treatment plan may help prevent resistance and reduce the side effects associated with prolonged drug exposure, ultimately improving the patient's quality of life and long-term survival prospects.³¹

Current therapy options for brain tumors administered individually only target a fraction of the tumor cell population, leading to incomplete eradication and allowing for the survival of resistant cell subpopulations that will continue to acquire aggressive mutations.^{32,33} The complexity and heterogeneity of tumors have made curing cancer a monumental task in the past. However, with advancements in technology and ongoing drug development efforts, the potential for combination therapy to target multiple aspects of tumor biology is increasing. By addressing different components of the tumor microenvironment and targeting diverse pathways, combination therapy holds the promise of more effectively eradicating a larger proportion of tumor cells, leading to prolonged survival and improved outcomes for patients with brain cancer.

Challenges for the Future of Brain Cancer Treatments

One of the major challenges in developing drugs that effectively target the brain is the vast amount of funding required to explore the intricate and complex nature of this organ. The brain is composed of a myriad of different cell types, each with its own unique

functions and interactions. As we continue to uncover more about how the brain operates, creating drugs that can effectively enter the brain and manipulate physiological conditions becomes increasingly challenging. Additionally, the BBB presents a significant hurdle in drug delivery to the brain, as it restricts the passage of many substances from the bloodstream to the brain. This further complicates the development of drugs that can effectively target brain tumors and drives the cost of drug development to levels that limit the availability of successful drug candidates to the patients who need them most.³⁴

Translating benchtop experiments to the tumor microenvironment within the brain is also a major obstacle in brain cancer treatment. The current technology available is limited in its ability to accurately replicate the complex conditions present in the brain. Artificial environments often fail to recapitulate the intricate interactions between different cell types and the unique characteristics of the brain tissue.³⁵ Without a reliable model of the brain tumor microenvironment, it is difficult to accurately predict how potential drug candidates will behave within the brain in a clinical setting.

Despite these challenges, the field of brain tumor treatment has seen exponential growth in recent years. With continued research and funding, the potential for success in developing effective treatments for brain cancer is limitless. Compared to decades ago, we now have a much better understanding of the brain and its complexities, which has opened up new avenues for innovative treatments and therapies. By investing in research and development in this field, we can overcome the current challenges and pave the way for more effective brain cancer treatments in the future.

Conclusion

The brain, with its intricate network of cells and functions, remains one of the most complex organs in the human body. This complexity has posed significant challenges in developing pharmaceuticals that can effectively cross the BBB and target brain tumors. Despite these obstacles, the field of brain tumor treatment has made significant progress over the years, including research on young patient populations with brain cancer. With advancements in early detection methods and better treatment options, we have come a long way from the limited options available for brain cancer diagnosis and treatment several decades ago. Brain tumors remain the most prevalent in children and AYA, underscoring the importance of continued research and innovation in this area.

While chemotherapies and some targeted therapies have been developed to treat cancer progression in the brain, they often fall short in reducing tumor burden. However, the incorporation of immunotherapies in brain tumor treatment has shown promising results, with the ability to not only halt progression but also shrink tumors in the brain.

Moving forward, the key lies in carefully combining multiple therapy options to maximize efficacy and

minimize costs associated with treatment. From pediatrics to geriatrics, making brain cancer treatment more widely available and effective for patients with diverse clinical presentations can bring hope to an area of cancer research that has long been in need of breakthroughs. The future of brain cancer treatment is bright, and with continued dedication and innovation, we can improve outcomes and quality of life for all patients facing this challenging disease.

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