Glioblastoma: current challenges and future horizons

NEURO-ONCOLOGY IN ASIA

Primary brain tumours are amongst the most feared cancers to date. Although rare, they impose a tremendous burden on healthcare systems because of their high rates of morbidity and mortality.[1,2] Globally, the age-standardised incidence rate (ASIR) of primary brain tumours is 4.63 per 100,000 person-years.[1,2] Data on primary brain tumours in Singapore are limited, with local institutes reporting frequencies of 7% to 9% of all operated primary central nervous system tumours.[3,4] However, in Asia, ASIR and disability-adjusted life-years have risen since 1990, and this is expected to increase over the next 25 years.[5] Although neuro-oncology in Asia has been developing rapidly to address these challenges, it is still highly disparate. High-resource centres, such as those in Singapore, Japan, South Korea, Taiwan, Hong Kong and the major cities of China and India, have access to advanced magnetic resonance imaging, awake surgery and chemoradiotherapy. However, many middle- and low-income nations face a severe shortage of qualified specialists, appropriate imaging and treatment facilities, and healthcare funding.[6] Even with a clear recognition of the shift towards molecularly guided glioma care, many institutions lack basic access to routine molecular assays, making the implementation of precision neuro-oncology difficult.[7] Apart from the lack of clinical resources, research productivity is another key factor. Despite a steady rise in neuro-oncology publications over the past two decades, research output from Asia remains substantially lower than that of Western countries, with much of the literature concentrated within a small number of academic medical centres.[8] This disparity is further compounded by the predominance of individuals of European ancestry in existing genomic datasets, limiting the applicability and generalisability of current treatment approaches for Asian populations.[9]

Among primary brain malignancies in adults, glioblastoma (GBM) is the deadliest and the most common. According to the 2021 World Health Organization (WHO) Classification of Tumours of the Central Nervous System (5th edition), GBM is defined as an isocitrate dehydrogenase (IDH)-wildtype, WHO Grade IV diffuse astrocytic glioma.[10] The incidence of GBM varies worldwide, with the Central Brain Tumour Registry of the United States reporting rates of about 14% of all brain tumours and 50% of all malignant brain tumours.[1] Despite a century of work, GBM remains a devastating disease with a dismal prognosis. This commentary delves into current challenges, novel solutions and attempts to address a fundamental question: Will there ever be a cure for brain cancer?

MECHANISMS OF RESISTANCE

Why is GBM so challenging to treat [Figure 1]? The main reason lies in its profound heterogeneity and immunoprivileged nature. Unlike many cancers that are driven predominantly by alterations in a single gene or pathway, GBM is characterised by multiple dysregulated oncogenic and tumour suppressor pathways. This molecular complexity creates redundant signalling networks and partly explains the limited efficacy of therapies targeting individual mutations. Furthermore, GBM is thought to arise from glioma stem cells (GSCs).[11,12] In addition to heightened signalling pathways, enhanced repair capabilities and migratory tendencies, GSCs impart a significant degree of intratumoural and intertumoural heterogeneity through clonal evolution and cancer stem cell models.[13] Consequently, no two GBMs are biologically identical, and even within a single tumour, multiple genetically and phenotypically distinct cell populations may coexist. This antigenic heterogeneity enables immune evasion and facilitates tumour repopulation following therapeutic pressure.

Beyond tumour heterogeneity, the immuno-privileged ecosystem of GBM presents another major therapeutic barrier, largely mediated by the blood–brain barrier (BBB) and the tumour microenvironment (TME). The highly selective BBB physically protects GBM from various drugs and restricts immune cell trafficking to the tumour bed. The GBM TME is a hostile, heterogeneous ecosystem with multiple dysregulations in cell signalling, metabolism and angiogenesis. Its most striking feature is its profound degree of immunosuppression. Tumour and stromal cells secrete inhibitory cytokines, driving tumour-associated macrophages and T-cell exhaustion. This enables immune evasion and unopposed tumour growth.[14]

NOVEL SOLUTIONS

Today's standard of care, largely thanks to the work of Stupp *et al*. in 2005, involves maximal safe surgical resection followed by radiotherapy and concomitant chemotherapy with the alkylating agent, temozolomide.[15] An exciting adjunct to this regimen is the use of tumour-treating fields. The Optune device (Novocure, Baar, Switzerland) is a non-invasive, portable and locoregional system that emits low-intensity, intermediate-frequency and alternating electrical fields through scalp transducers. These electrical fields disrupt spindle fibre formation in rapidly proliferating GBM cells, resulting in mitotic catastrophe and cell death.[16,17] Although trials have shown improvement in progression-free survival, even in the context of recurrence, the

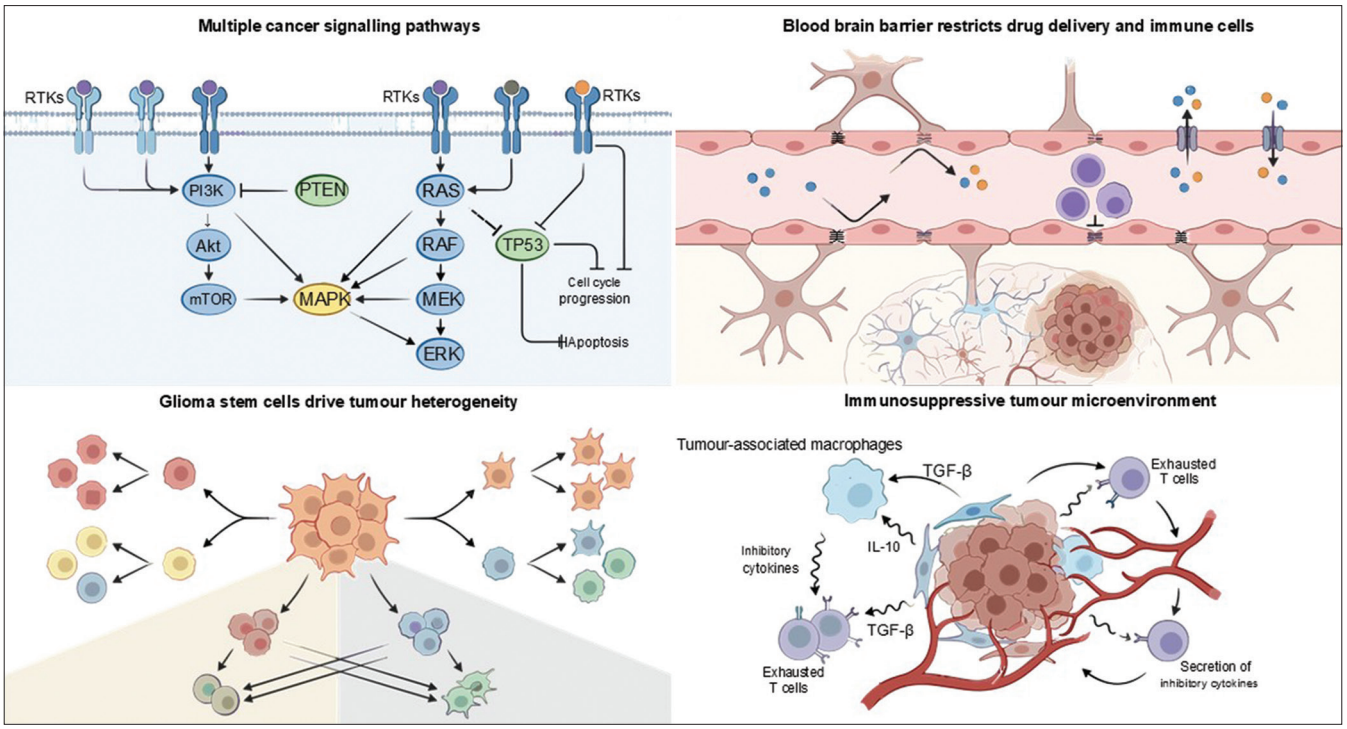

Figure 1: Mechanisms of therapeutic resistance in glioblastoma. IL-10: interleukin-10, MAPK: mitogen-activated protein kinase, mTOR: mammalian target of rapamycin, PI3K: phosphoinositide 3-kinase, PTEN: phosphatase and tensin homolog, RTK: receptor tyrosine kinase, TGF-β: transforming growth factor-beta [Created with FigureLabs.AI]

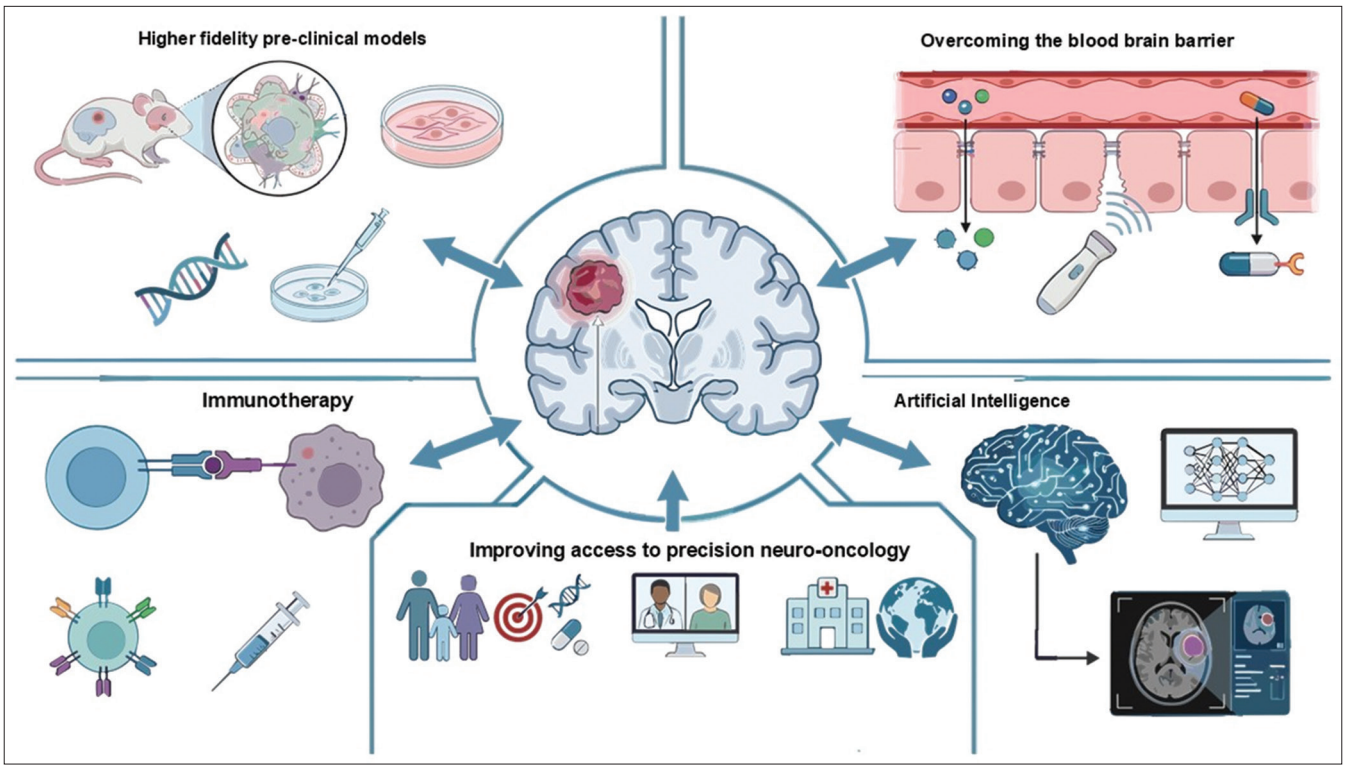

Figure 2: Novel solutions for glioblastoma treatment. [Created with FigureLabs.AI]

increase is marginal.[18,19] Overall, the median survival for GBM is 12–15 months, with fewer than 5%–10% of patients surviving beyond 5 years.[1] These sobering outcomes underscore the urgent need for more effective therapies [Figure 2], beginning with a deeper understanding of tumour biology. A major limitation lies in current preclinical models, which often rely

on poorly representative *in vitro* systems or xenografts that fail to fully capture the complexity of human GBM. Even with more sophisticated orthotopic brain tumour models, the lack of critical features, such as a functioning BBB, results in failure to recapitulate the actual disease process. To facilitate a more comprehensive understanding of GBM pathogenesis, efforts should focus on generating advanced genetically engineered mouse models and patient-derived xenografts. These models must accurately represent GBM at the phenotypical and molecular levels. They should also allow for the integration of conventional treatments to ascertain whether new therapeutics confer a meaningful survival benefit beyond that achieved with existing standards of care.[20]

Other therapeutic strategies aim to overcome the BBB, which is the main obstacle limiting effective drug delivery to GBM. Multiple approaches to improve BBB permeability are currently under investigation, in particular, the use of laser interstitial thermal therapy and focused ultrasound. Laser interstitial thermal therapy is a minimally invasive technique that delivers hyperthermic energy to a target through a fibre-optic probe. Controlled thermal ablation induces localised coagulative necrosis while protecting the adjacent healthy tissue. Laser interstitial thermal therapy also transiently disrupts the BBB and promotes the release of damage-associated molecular patterns, converting 'cold' tumours into 'hot', immunologically reactive ones.[21] This treatment holds promise for deep-seated or recurrent tumours, with 12-month survival rates of up to 65% reported in selected patients with high performance scores.[22] Focused ultrasound uses acoustic cavitation, a technique employing low-intensity ultrasound waves and oscillating microbubbles to temporarily relax endothelial tight junctions. This enables large-molecule chemotherapeutics to be delivered in higher concentrations, improving local tumour control.

Beyond surgical techniques, increasing attention has been given to the use of neural stem cells and mesenchymal stem cells as therapeutic delivery vectors. Owing to their intrinsic tumour-tropic and migratory properties, these cells can home to GBM sites and serve as versatile carriers for a range of therapeutic payloads, including cytotoxic agents, enzyme-prodrug systems, gene-editing tools and immunomodulatory molecules. Although further studies are required to establish their long-term safety and clinical efficacy, stem-cell-based therapies represent a promising strategy for achieving more targeted treatment delivery while potentially minimising systemic toxicities.[13]

Despite the use of next-generation sequencing to identify novel targets, most targeted monotherapies and immune checkpoint inhibitors for GBM have been unsuccessful. This is due to several reasons, including multiple oncogenic pathways driving gliomatogenesis, antigenic heterogeneity, reduced neoantigen burden, impaired antigen presentation and active immunosuppression. Currently, trials investigating both cell-based and non-cell-based immunotherapies are ongoing. Adoptive cellular therapies, such as dendritic cell vaccines and chimeric antigen receptor T-cells, have been shown to broaden T-cell responses to GBM antigens and to confer survival benefit in patients with recurrent GBM.[23-25] Oncolytic viruses, such as poliovirus and herpes simplex virus, can lyse tumour cells and release antigens. When combined with stimulatory cytokines, they can reprogram the TME to an immunologically reactive state.[26] Increasingly, it appears unlikely that a single therapeutic target will be sufficient for GBM. Future progress will likely depend on synergistic multimodal approaches evaluated through adaptive clinical trial designs, which may better address the heterogeneous and evolving nature of the disease.

The rise of artificial intelligence (AI) brings new opportunities across the entire neuro-oncology spectrum of care. An up-and-coming field is radiogenomics, which utilises quantitative imaging features to predict genetic traits. Studies have reported algorithms with diagnostic accuracy of 85%–90% in predicting the molecular status of gliomas, potentially offering a safer path towards prognosis and treatment when surgery is not feasible. Moreover, radiogenomics can also be employed to assess and predict treatment response. Together with brain tumour segmentation, this enables the identification of subtle structural and functional changes to better predict disease progression or even distinguish true progression from pseudoprogression and radiation necrosis.[27] Intraoperatively, AI can also accelerate the diagnosis of tumour samples. Training AI with whole-slide images and Raman spectroscopy results in a form of 'digital neuropathology', allowing for rapid diagnosis and assessment of tumour margins to guide surgical resection. Beyond diagnosis, AI has the potential to integrate clinical, radiological, molecular, genomic and treatment data into a longitudinal flow of information that accompanies the patient throughout their entire journey. This could enable an unprecedented level of precision in clinical decision-making, facilitating the selection of the most appropriate therapies and improving the overall management of patients with GBM.[28]

CONCLUSION

In conclusion, GBM remains a highly complex and heterogeneous malignancy characterised by profound therapeutic resistance. Although maximal safe resection followed by chemoradiotherapy remains the current standard of care, meaningful advances will likely require integrating molecular biology, immunotherapy and AI-driven approaches. Equally important are efforts to improve equity in neuro-oncology through regional collaboration, workforce development and investment in diagnostic infrastructure. Ultimately, GBM management must evolve towards a dynamic, personalised and multimodal approach tailored to the unique biology of each patient's tumour.

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