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General review

Literature review: CAR T-cell therapy as a promising immunotherapeutic approach for medulloblastoma

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ABSTRACT

Medulloblastoma (MB) accounts for approximately 20–25% of all childhood brain tumours and 63% of intracranial embryonic tumours, with an annual incidence of around 5 cases per million in the paediatric population. This high-grade neuroepithelial tumour of the posterior fossa can develop at any age during childhood, adolescence and even adulthood, often spreading via cerebrospinal fluid. While most MB cases are sporadic, they can be associated with genetic predisposition syndromes. Although these genetic mutations present potential therapeutic targets, the limited number of mutations and few existing therapies aimed at these neoantigens pose significant challenges. Despite aggressive multimodal treatment approaches, approximately 30% of patients ultimately succumb to MB, and survivors frequently face long-term side effects that severely impact their quality of life. MB harbours unique molecular factors, necessitating careful consideration of therapeutic targets such as the blood-brain barrier, tumour microenvironment, and the differing responses of cancer stem cells versus bulk tumour tissue. Conventional treatment typically involves maximal safe resection, risk-adapted chemotherapy, and/or radiation craniospinal irradiation. While there is general agreement on the benefits of chemotherapy for MB patients, adverse side effects remain prevalent, underscoring the need for alternative therapeutic strategies. Given the heterogeneous nature of MBs and the lack of salvage treatment, immunotherapy has emerged as a promising novel treatment avenue. This personalized approach aims to enhance specificity and potentially reduce side effects. Among these innovative methods, adoptive cell therapy, particularly chimeric antigen receptor T (CAR T) cell therapy, shows great promise. This review will explore the potential of CAR T-cell therapies in targeting MB, building on their successful application in other solid tumours.

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1. Abbreviations

CAR	chimeric antigen receptor
CNS	central nervous system
CRS	cytokine release syndrome
EPHA	ephrin type-A receptor 2
GBM	glioblastoma
HER2	receptor tyrosine-protein kinase ERBB2
MB	medulloblastoma
MHC	major histocompatibility complex
OS	overall survival
NKG2D	natural killer group 2D
SHH	sonic hedgehog
TCR	T-cell receptor
WNT	wingless related integration

2. Introduction

Medulloblastoma (MB) represents approximately 20% of all childhood brain tumours and 63% of intracranial embryonic tumours [1]. In high-income countries (HICs), MB accounts for 20% of paediatric brain tumours, while data from low- and middle-income countries (LMICs) show significant variation in incidence rates, ranging from 6% to 50% [2,3]. These tumours can develop at any age during childhood and even into adulthood, with an overall annual incidence of approximately 5 cases per 1 million in the paediatric population. Approximately 75% of MBs occur in children under the age of 10, with incidence peaking in children 1–4 and 5–9 years of age [1]. MB is categorized as an embryonal neuroepithelial tumour of the posterior fossa and is a high-grade tumour that can disseminate via cerebrospinal fluid (CSF). Although the exact cause is unknown, a small percentage of MBs are related to genetic changes and can be passed down through families.

MB consists of a group of histologically and molecularly diverse posterior fossa tumours [1,3,4]. These tumours are characterized by undifferentiated, small round blue cells with mild-to-moderate nuclear pleomorphism and high mitotic counts. There are four recognized histological variants: (1) classic, (2) desmoplastic or nodular, (3) MB with extensive nodularity (MBEN), and (4) large-cell or anaplastic (LCA). Additionally, four molecular subgroups have been identified: wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. Molecular subgrouping plays a significant role in treatment decisions and is a key predictor of prognosis [5].

The epidemiological profile, clinicopathological features, and survival outcomes of MB in South Africa's diverse population remain largely unknown. Risk stratification of children with MB is typically performed using the modified Chang system, which categorizes patients into standard- and high-risk groups. Standard risk is defined by the following criteria: age $\geq$ 3 years at diagnosis, residual tumour $<$ 1.5 cm^2 post-resection, absence of tumour cells in CSF, no evidence of leptomeningeal spread on computed tomography (CT) or magnetic resonance imaging (MRI), and classic or desmoplastic histology. High-risk disease is diagnosed when any of the following conditions are present: age $<$ 3 years, residual tumour $>$ 1.5 cm^2 post-surgery, CSF positive for tumour cells, leptomeningeal spread on CT/MRI, or large cell/anaplastic (LCA) histology [5,6].

Although most cases of MB arise sporadically, they can be associated with multiple genetic predisposition syndromes, as mentioned, especially within the SHH-activated group. While these genes could be exploited as therapeutic targets, the number of mutations is generally relatively low and few therapies targeting these tumour neoantigens currently exist. Syndromes associated with MB include Li-Fraumeni syndrome, Turcot syndrome, some types of Fanconi anaemia, and Gorlin syndrome [7].

Within the first few years of diagnosis, the mortality rate is approximately 15%, however, cure rates can reach up to 60% with therapeutic approaches [8]. MB is currently treated with maximal safe resection, risk adapted chemotherapy, and/or craniospinal irradiation (CSI). With a multimodal approach and appropriate risk stratification, long-term survival rates have improved [9]. Despite these advancements, treatment-related neurocognitive and endocrinological effects continue to pose significant challenges, fuelling the ongoing pursuit of improved therapeutic options [10]. Even with aggressive multimodal therapy, approximately 30% of patients eventually succumb to the disease, while survivors endure long-term side effects that profoundly affect their quality of life [11].

As such, this review aims to provide an overview of the potential of Chimeric antigen receptor (CAR) T-cell therapy as an immunotherapeutic strategy for MB. We begin by outlining the broader challenges in oncology and the limitations of conventional treatments, followed by a discussion on the development and mechanism of CAR T-cell therapies. Lastly, examining current research on CAR T-cell applications in MB and assessing their associated limitations and toxicities. Through this review, we aim to highlight both the promise and the ongoing challenges of translating CAR T-cell therapy into effective clinical interventions.

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science up to 2024. Search terms included: ''CAR T-cell'', ''chimeric antigen receptor'', ''medulloblastoma'', ''immunotherapy'', ''paediatric brain tumour'', and combinations thereof. Articles were screened based on relevance to CAR T-cell therapy in MB, publication in English, and accessibility of full text. Review articles, preclinical studies, and clinical reports were considered. Studies were excluded if they were unrelated to immunotherapy, focused solely on other tumour types, or lacked primary data.

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3. Challenges in modern oncology

MB is fundamentally distinct from other types of cancer, particularly peripheral tumours [12]. Several factors—such as the blood-brain barrier (BBB), the microenvironment, and the varying responses of cancer stem cells compared to the bulk tumour tissue—must be considered when considering therapy for MB [13]. Additionally, unfavourable outcomes often observed in LMICs may be explained by higher rates of metastatic disease at diagnosis and different underlying biology in young children. The widespread reluctance to expose the immature brain to craniospinal radiotherapy and its significant long-term radiotherapy effects also contribute to the removal of sub-optimal tumours [3].

The BBB is often a key reason for the poor survival rates associated with brain tumours, as many current systemic treatments, apart from radiation, struggle to cross this barrier. The BBB consists of astrocytes, pericytes, and endothelial cells, forming a protective shield that prevents the entry of toxins and other harmful substances into the brain tissue. Additionally, brain tumours disrupt the BBB to form the blood-tumour barrier (BTB), which has heterogenous perfusion and permeability throughout the tumour and hinders the delivery of common chemotherapeutics [14].

In South Africa, the proportion of high-risk cases significantly exceeds reports from HICs, where the ratio typically favours standard-risk cases. This discrepancy likely reflects multiple contributing factors, including a higher prevalence of patients under three years old, delayed presentation due to socioeconomic challenges and limitations in public healthcare, delays in definitive diagnosis and multimodal management, and slower progress in diagnostic and treatment strategies [3].

Addressing these barriers is critical for advancing treatment options and improving outcomes for patients with MB. The aim of this review is to explore the potential of novel therapies in targeting MB, to improve patient outcomes.

4. Traditional treatment and limitations

As previously mentioned, the treatment of MB requires a multidisciplinary approach and varies based on risk stratification - including histopathological subtype, age at diagnosis, staging, residual disease, MYC status, and molecular subgrouping [1]. Conventional treatment for MB involves maximal safe resection, risk adapted chemotherapy, and radiation therapy [15]. Surgery is typically performed first, with the prognosis heavily influenced by the extent of resection. Following surgery, the entire craniospinal axis is irradiated, which can lead to severe adverse effects, including neuroendocrine dysfunction, growth abnormalities, neurocognitive impairments, infertility, secondary cancers, and a reduced quality of life. Due to these risks, infants, who are particularly vulnerable to severe intellectual disabilities, are often treated with strategies that avoid radiation [16]. Studies attempting to reduce or eliminate radiation have proven ineffective for treating MB, highlighting the challenge of balancing survival with neurocognitive outcomes. While adjuvant chemotherapy has significantly improved survival rates, it remains unable to cure over 30% of patients within five years [15].

In low-risk patients, those without metastases at diagnosis, minimal residual tumour post-resection, and classic histology progression-free survival (PFS) and overall survival (OS) rates exceeding 80% have been achieved using craniospinal radiation at 23.4 Gy with a posterior fossa boost of up to 54 to 55.8 Gy, combined with adjuvant vincristine [17]. Post-radiation, maintenance chemotherapy typically includes vincristine, cisplatin, and either cyclophosphamide or lomustine [18]. In contrast, high-risk patients, characterized by metastases at diagnosis, residual tumours larger than 1.5 cm, or large cell/anaplastic histology, continue to experience sub-optimal outcomes despite treatment advances. Although OS has improved from 60% to 70% over the past decade due to high-dose chemotherapy and alternative fractionated radiotherapy, the long-term effects of these treatments remain unknown [19]. High-risk patients receive 36 to 39.6 Gy of radiation followed by four cycles of high-dose chemotherapy with agents such as cyclophosphamide, cisplatin, carboplatin, and vincristine, accompanied by autologous peripheral blood stem cell rescue [13,20]. Although there is no established standard chemotherapy regimen, there is consensus that chemotherapy benefits MB patients. However, adverse side effects are still prevalent, highlighting the need for alternative treatment strategies to reduce escalation.

Additionally, relapses of these tumours are often significantly harder to treat than the initial tumour, particularly in older children who have already undergone multimodal therapy. Relapses are challenging due to their potential for distant spread, especially in the non-WNT/non-SHH subgroup [15]. Conventional treatments for relapsed MB, such as re-resection, re-irradiation, and high-dose chemotherapy, rarely yield successful outcomes, with survival rates often below 10%. Recent research indicates that while the molecular subgroup of the relapsed tumour remains the same, actionable changes present in the primary tumour may not be found at relapse, suggesting tumour evolution. Late recurrences, occurring five or more years after diagnosis, are uncommon and predominantly found in subgroup VIII of the non-WNT/non-SHH class [13,21]. Other late recurrences are more likely related to treatment effects rather than the primary tumour's relapse. These secondary, often high-grade, glial tumours are generally resistant to treatment [18]. Re-resection and pathological diagnosis are crucial in these cases.

Due to the heterogenic nature of MB tumours, immunotherapy has recently been the primary focus of novel therapy development. Over the past twenty years, immunotherapy has been extensively explored and implemented clinically in various cancer treatments, leading to the development of numerous clinical immunotherapeutic options [22]. Immuno-oncological intervention aims to harness and enhance the body's immune system to detect and eliminate tumours. This approach can be individualised for each patient, increasing specificity and potentially reducing side effects. These methods include adoptive cell therapy including chimeric antigen receptor T (CAR T) cells, immunomodulators, vaccines and antibodies targeting immune checkpoints. Studies have also concluded that it is important to consider the molecular differences among the four MB subgroups, as these may

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significantly impact the immunological tumour microenvironment (TME) and the effectiveness of various immunotherapy strategies [23]. These new therapies must specifically target malignant cells while minimizing off-target cytotoxicity, a common issue with traditional chemotherapeutics, and maintain a potent, sustainable cytotoxic effect on cancer cells to reduce the risk of recurrence. CAR T-cells have the potential to achieve these objectives. This review explores the potential of CAR T-cell therapies in targeting MB, building on their successful application in other solid tumours.

5. Immunotherapy: CAR T-cell therapies

5.1. *Overview*

CAR T-cells represent a type of adoptive cell therapy utilized in immunotherapies [24]. Initially approved by the US Food and Drug administration (FDA) in 2017 for the treatment of haematological malignancies, CAR T-cells have also demonstrated efficacy in numerous preclinical and clinical studies for solid tumours, including glioblastoma (GBM), high grade gliomas, MB, and ependymoma [25,26]. CARs are synthetically created receptors enabling T-cells to recognize and target specific cells based on expression of a target antigen. CARs are created by fusing a single-chain variable fragment (scFv) of a target specific antibody with the T-cell receptor (TCR) signalling domain CD3 [27]. This combination enables T-cells to recognize antigens in a manner similar to antibodies, thereby activating their cytotoxic activity without the need for antigen presentation by the major histocompatibility complex (MHC) [28]. Despite this, co-stimulation remains essential for the T-cell to effectively carry out its cytolytic function, proliferate, and persist in the local microenvironment [29]. In natural settings, these co-stimulatory signals are provided by antigen-presenting cells. However, in engineered CAR T-cells, multiple co-stimulatory domains can be incorporated into the construct to enhance T-cell functionality [29,30]. For CAR T-cell applications in cancer treatment, the engineered target should ideally be exclusively present on tumour cells and absent from normal cells, thereby minimizing off-target therapeutic effects [24]. However, several challenges limit the efficacy of CAR T-cell therapy in solid tumours, including challenges in trafficking to the tumour site, the presence of an immunosuppressive environment, toxicity, and tumour antigen heterogeneity [31]. CAR T-cell infusion to the brain, which bypasses the BTB, can be administered through the bloodstream, CSF, or directly into the tumour cavity. Brain tumours, particularly GBM, are currently the most common solid tumours being evaluated in clinical trials for CAR T-cell efficacy, and early results have shown promising outcomes [32]. Currently, six different CAR T-cell products have been approved by the FDA: tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, brexucabtagene autoleucel, idecabtagene vicleucel, and ciltacabtagene autoleucel [33].

5.2. *Mechanism of action*

In a typical T-cell response, a naive T-cell is activated when its TCR binds to an MHC complex displaying a foreign peptide, in conjunction with co-stimulation from an antigen-presenting cell (APC). The activated T-cell then proliferates and is primed to execute effector functions upon re-encountering the same antigen on a target cell. This interaction forms an immunological synapse between the T-cell and target cell, which includes not only the TCR-MHC complex but also adhesion molecules such as lymphocyte function-associated antigen-1 (LFA-1) binding to its ligand on the target cell. These interactions transmit signals that trigger the release of effector molecules, which can be either cytotoxins inducing apoptosis in the target cell or cytokines with various functions. Additionally, TCR signalling shifts the metabolism of T-cells from oxidative phosphorylation to glycolytic and glutaminolytic pathways. Chronic stimulation can lead to T-cell exhaustion, characterized by inhibiting proliferation and effector functions, with exhausted T-cells showing suppressed oxidative phosphorylation and glycolysis [34].

Similar to normal T-cells, CAR T-cells execute effector functions against target tumour cells. However, the interactions and synapses involved in CAR T-cell expansion, cytotoxicity, cytokine release, and persistence can differ from those in conventional T-cells (Lee et al., 2019). These variations are influenced by the CAR design and the expression of the target antigen on tumour cells. The effectiveness of CAR T-cells can also be affected by manufacturing conditions, characteristics of the target tumour cell, and the TME [33].

Unlike conventional T-cells, most CARs have a recombinant receptor that binds directly to a tumour antigen on the target cell surface, bypassing the need for MHC presentation. This enables CAR T-cells to recognize a broader range of targets with significantly higher binding affinity and specificity [35]. CARs are composed of an antigen-binding domain (scFv), a hinge and transmembrane domain linking the extracellular domain to the intracellular signalling domain(s), and an intracellular signalling domain with an activation domain (usually CD3 zeta (ζ)). Second- and third-generation CARs incorporate one or two co-stimulatory domains (such as CD28 and/or 4-1BB) to enhance intracellular signalling. Each component of the CAR plays a specific role in antigen recognition and CAR T-cell activation, impacting the downstream effector functions [36].

CAR T-cells are activated when their antigen-binding domain identifies and binds to its target antigen. This interaction causes CAR molecules on the T-cell surface to cluster, leading to the immobilization of the CAR molecule and the formation of an immune synapse. This stable connection is crucial for initiating tumour cell killing, as it triggers lysis of the target cell by the effector T-cell [37]. CAR T-cells are engineered to autonomously recognize and destroy target cells, while also promoting T-cell expansion and differentiation—key processes that enhance CAR T-cell efficacy by increasing tumour cell targeting and ensuring long-term tumour control. However, excessive activation of CAR T-cells can result in toxicity from cytokine release or reduced efficacy due to diminished persistence. The level of CAR T-cell activation is influenced by factors such as immune synapse formation, target antigen density, CAR affinity for the target antigen, and the strength of signal transduction [33]. In solid tumours, where target antigens are frequently overexpressed on tumour cells but are also present at lower levels on normal

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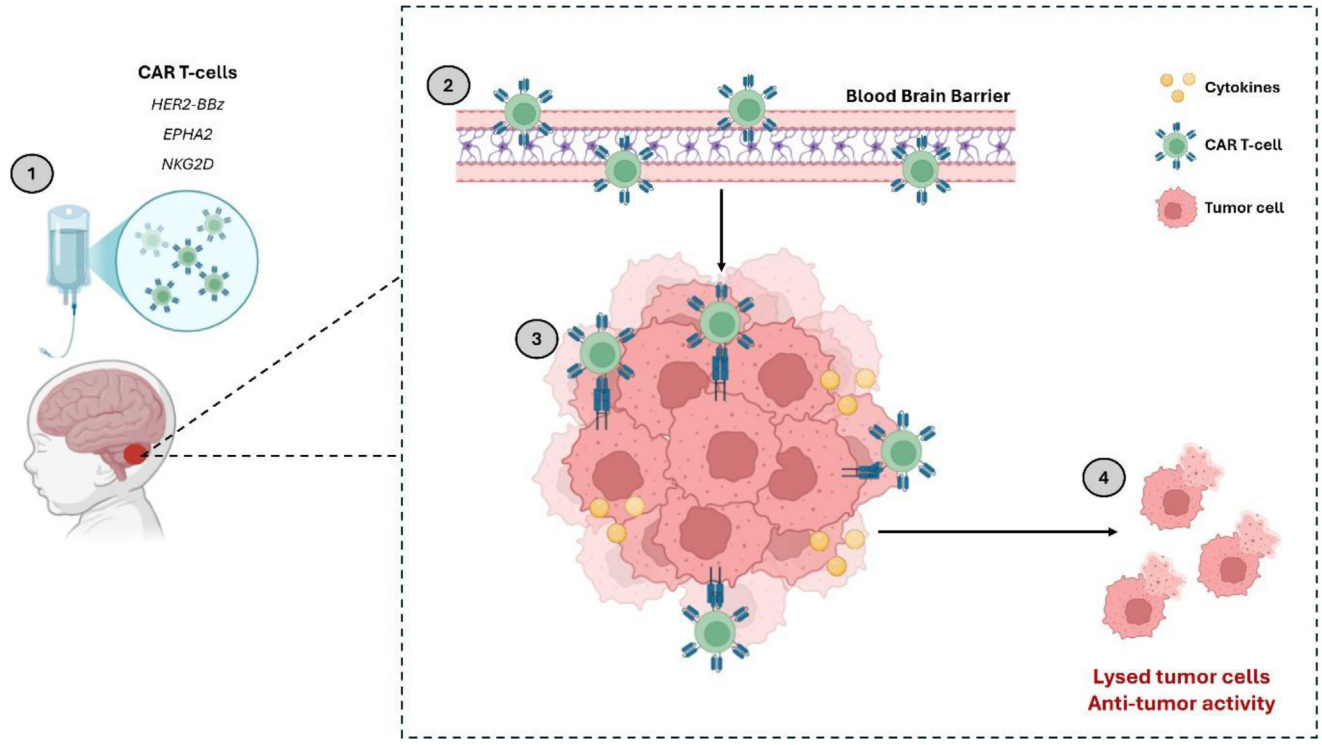

Fig. 1 – CAR T-cell therapies, including HER2-BBz, EPHA2, and NKG2D, hold promising potential for treating paediatric/adolescent MBL. (1) Intravenous administration: CAR T-cells are infused into the paediatric/adolescent patient through an intravenous drip, allowing the modified immune cells to circulate in the bloodstream; (2) Crossing the blood-brain barrier: once in circulation, the CAR T-cells are capable of crossing the BBB, a critical step for targeting MBL; (3) Targeting tumour cells in the TME: the CAR T-cells specifically recognize and bind to their corresponding receptors—such as HER2, EPHA2, or NKG2D ligands—expressed on the surface of tumour cells in the TME and (4) Tumour cell lysis: upon binding, the CAR T-cells become activated, releasing cytotoxic agents that lead to tumour cell destruction, thereby demonstrating their anti-tumour activity (made with Biorender.com).

cells, it's crucial to design CAR T-cells that can differentiate between these varying antigen density thresholds (Fig. 1).

6. Promising CAR T-cell therapies

6.1. *HER2-BBz-CAR T-cells*

Receptor tyrosine-protein kinase ERBB2 (HER2) is a prominent target for immunotherapy, as it is overexpressed in various adult and pediatric cancers, including about 40% of MB cases [38,39]. CAR T-cell therapy targeting HER2 in MB has been studied most intensively in the past years. The presence of HER2 on MB tumours is linked to significantly poorer overall and progression-free survival outcomes [40]. Additionally, ERBB2 protein is absent in normal brain tissue, making it an appealing target for therapeutic interventions in these tumours [41]. CAR T-cell therapy offers a promising strategy for targeting HER2-expressing tumours by directly eliminating cancer cells through T-cell cytotoxicity, rather than relying on antibody-dependent cell-mediated cytotoxicity [42]. Adoptive transfer of CAR T-cells has shown promise in mouse models of MB. In earlier preclinical studies, first-generation HER2-CAR T-cells, which included only CD3ζ signalling without a co-stimulatory domain, resulted in only temporary tumour regression in an orthotopic xenograft mouse model of MB [43]. However, newer generations of CAR T-cells that incorporate co-stimulatory domains have demonstrated enhanced immune proliferation and sustainability in other tumour models, leading to improved cytotoxicity [42]. Currently, HER2-CARs are being tested in clinical trials for the treatment of GBM and sarcomas, where they have been found to be safe and well-tolerated [44]. Nellan et al. found that second-generation HER2-CAR T-cells, which include CD3ζ and 4-1BB signalling motifs, exhibit strong in vitro anti-tumour activity against MB cell lines and effectively eradicate tumours in multiple orthotopic xenograft mouse models of MB [39]. The study also demonstrated that very low doses of HER2-CAR T-cells can achieve complete and lasting regression of established CNS tumours when administered regionally. Furthermore, these CAR T-cells were able to persist at low levels in both the brain and peripheral blood of treated mice for an extended period following tumour clearance.

Another study has demonstrated robust anti-tumour responses in human xenograft models of $HER2^{+}$ breast cancer metastasis to the brain, after local intratumoural or regional intraventricular delivery of HER2-BBζ CAR T-cells [45]. The authors show that HER2-CARs with the 4-1BB co-stimulatory

domain provide better tumour targeting, reduced T-cell exhaustion, and enhanced proliferative capacity compared to HER2-CARs with the CD28 co-stimulatory domain. Local intracranial delivery of HER2-CARs exhibited strong in vivo anti-tumour activity in orthotopic xenograft models. Additionally, regional intraventricular delivery of HER2-CAR T-cells resulted in robust anti-tumour efficacy for the treatment of multifocal brain metastases.

Cheng et al. studied T-cells engineered with an autocrine PD-L1 scFv and a 4-1BB-containing CAR to evaluate their anti-tumour activity and exhaustion in vitro and in a xenograft cancer model using NCG mice (triple-immunodeficient mice) [46,47]. The CAR T-cells with the autocrine PD-L1 scFv antibody demonstrated enhanced anti-tumour activity in both solid tumours and hematologic malignancies by blocking the PD-1/PD-L1 signalling pathway. Importantly, they observed that CAR T-cell exhaustion was significantly reduced in vivo with the autocrine PD-L1 scFv antibody. Thus, the combination of 4-1BB CAR T-cells with the autocrine PD-L1 scFv antibody merges the benefits of CAR T-cells and immune checkpoint inhibition, enhancing anti-tumour immune function and CAR T-cell persistence, and potentially improving clinical outcomes for cell therapy [47]. Thereby highlighting the promising role of the 4-1BB signalling domain.

Similar to many cancer therapies, the use of CAR T-cells presents a double-edged sword. A 2010 case report highlighted safety risks with intravenous HER2-CAR-T cells. In this report, a 39-year-old colon cancer patient with liver and lung metastases received HER2-CAR T therapy. Five days later, the patient died from a cytokine storm caused by HER2 recognition on lung epithelial cells. This shows the critical need for targeting specific tumour antigens to ensure safety. Since HER2 is not expressed in healthy brain tissue, the risk of on-target, off-tumour effects in the brain is reported to be minimal [39].

In a recent phase I clinical trial (NCT03500991), interim results from three MB patients treated with intratumoural HER2-CAR T-cells were published [48]. Patient one received two treatment courses, while patients two and three completed three. None of the patients experienced dose-limiting toxicities, but adverse events included headache, pain, and fever, linked to elevated systemic C-reactive protein levels. Neuroimaging showed progressive disease in patients one and three, while patient two had stable disease. The authors suggest that locoregional HER2-CAR T-cell administration may be feasible and that evaluating CAR T-cell activity in the CNS is important, although larger studies are needed to assess clinical benefit in MB patients.

6.2. *EPHA2-specific CAR T-cell therapy*

Erythropoietin-producing hepatocyte receptor A2 (EphA2) is a receptor tyrosine kinase (RTK) involved in various developmental, physiological, and disease-related processes. It is significantly overexpressed in MB and GBM, while being minimally expressed in normal brain tissue, making it a promising target for CAR T-cell therapy development [49,50]. Chow et al. developed the first EphA2-specific CAR using the humanized EphA2 monoclonal antibody 4H5 [51,52].

In a study, Zhang et al., observed that EphA2-CAR T-cells stimulated by B-cells showed increased interferon-γ (IFN-γ) production, upregulated OX40 expression, enhanced anti-tumour activity, and reduced PD-1 expression. Next-generation sequencing (NGS) revealed upregulated genes involved in immune response, chemokine, and calcium signalling pathways, contributing to improved anti-GBM activity. Key genes such as *MEF2C*, *CD40*, *SYK*, and *TNFRSF13B*, which promote lymphocyte proliferation, were also upregulated. These findings highlight the role of B-cells in enhancing CAR T-cell

Table 1 – An overview of the therapeutic potential of CAR T-cell therapy.

1. HER2-BBz CAR T-cells			
Model	Cancer	Findings	Reference
In vitro	MB	Strong anti-tumour activity	[39]
In vivo		Eradicated tumours in mice	
		Low levels of CAR T-cells remain in the brain and blood	
Human Xenograft	Breast cancer with brain metastasis	Anti-tumour activity	[45]
In vivo	Breast and leukaemia	↓ T-cell exhaustion	[46,47]
In vitro		↑ Anti-tumour immune function	
2. EPHA2 CAR T-cells			
Primary tumour cells	GBM	Anti-tumour activity	[51]
		↓ PD-1	
		↑IFN- γ	
		↑ *MEF2C*, *CD40*, *SYK*, and *TNFRSF13B*	
In vitro	GBM	↑ Survival	[49]
		↑ CXCR1/2	
Clinical Trial (NCT03423992)	GBM	↓ Tumour size	[53]
		Grade 2 cytokine storm	
3. NKG2D CAR T-cells			
In vitro	MB	↓ Tumour cells	[54]
Primary cells		↑ Cytokines	
In vitro	GBM	Lysed GBM cells	[56]
Primary tumour samples		↑ Perforin and granzyme B	
In vitro	GBM	↑ Cytokines (TNFα, IFN-γ, IL-10, and IL-2)	[57]
		Lysed tumour cells	

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persistence and anti-tumour effects, providing a potential therapeutic avenue for EphA2-CAR T-cells in GBM treatment [49]. Similarly in another study, EphA2-targeting CAR T-cells were successfully activated and expanded by EphA2-positive tumour cells in vitro, significantly improving the survival of tumour-bearing mice. One CAR variant showed superior anti-tumour activity linked to increased CXCR-1/2 expression and optimal IFN-γ production. However, excessively high IFN-γ levels led to poor anti-tumour effects by upregulating PD-L1 in GBM cells. Combining these CAR T-cells with PD-1 blockade enhanced efficacy in tumour-bearing mice. Overall, both CAR T-cell types eliminated 20%–50% of GBM in xenograft models, indicating that a balanced combination of IFN-γ and CXCR-1/2 levels is crucial for assessing CAR T-cell anti-tumour efficiency (Zhang et al., 2024). Lin and co-authors reported the first-in-human trial of EphA2-redirected CAR T-cells in patients with EphA2-positive recurrent GBM (NCT03423992), involving three patients receiving an initial dosage of 1×10^6 cells/kg. The CAR T-cells were administered intravenously following a lympho-depletion regimen of fludarabine and cyclophosphamide. Two patients experienced grade 2 cytokine release syndrome (CRS) with pulmonary edema, which was resolved with dexamethasone, while no other organ toxicity was observed. CAR T-cell expansion was noted in both peripheral blood and cerebrospinal fluid for over four weeks, with one patient showing a temporary reduction in tumour size. Among the three patients, one had stable disease and two had progressive disease, with OS ranging from 86 to 181 days. The trial indicated that EphA2-redirected CAR T-cell infusion at this dose level is preliminarily tolerable with transient clinical efficacy, warranting further studies with adjusted dosing and infusion frequency [53].

Despite earlier successes, several models experience tumour recurrence. Combining EPHA2 CAR T-cell therapy with the chemotherapeutic azacytidine, resulted in complete tumour clearance and relapse-free survival in 40% of mice. However, although other mice exhibited significant reductions in tumour burden, they eventually relapsed [52].

6.3. *NKG2D-specific CAR T-cells*

NK group 2 member D activatory receptor ligands (NKG2DLs) are expressed on MB cell lines (Daoy and D341) and most primary MB tumour samples [54]. CAR T-cells targeting NKG2D ligands were tested in vitro with Daoy cells. These ligands effectively killed tumour cells and increased cytokine levels of TNF-α, IFN-γ, IL-10, and IL-2. These CAR T-cells were then used in mice with MB xenografts, successfully eliminating tumours without significant toxicity or organ damage.

One study confirmed high expression of NKG2DLs in human GBM cells, cancer stem cells, and tumour samples [54]. NKG2D-BBz CAR T-cells effectively lysed GBM cells and cancer stem cells in vitro, producing elevated levels of cytokines, perforin, and granzyme B. In vivo, these CAR T-cells significantly eliminated xenograft tumours without causing notable treatment-related toxicity in mice. Additionally, CAR expression did not affect cell proliferation, apoptosis, or genomic stability. A clinical trial

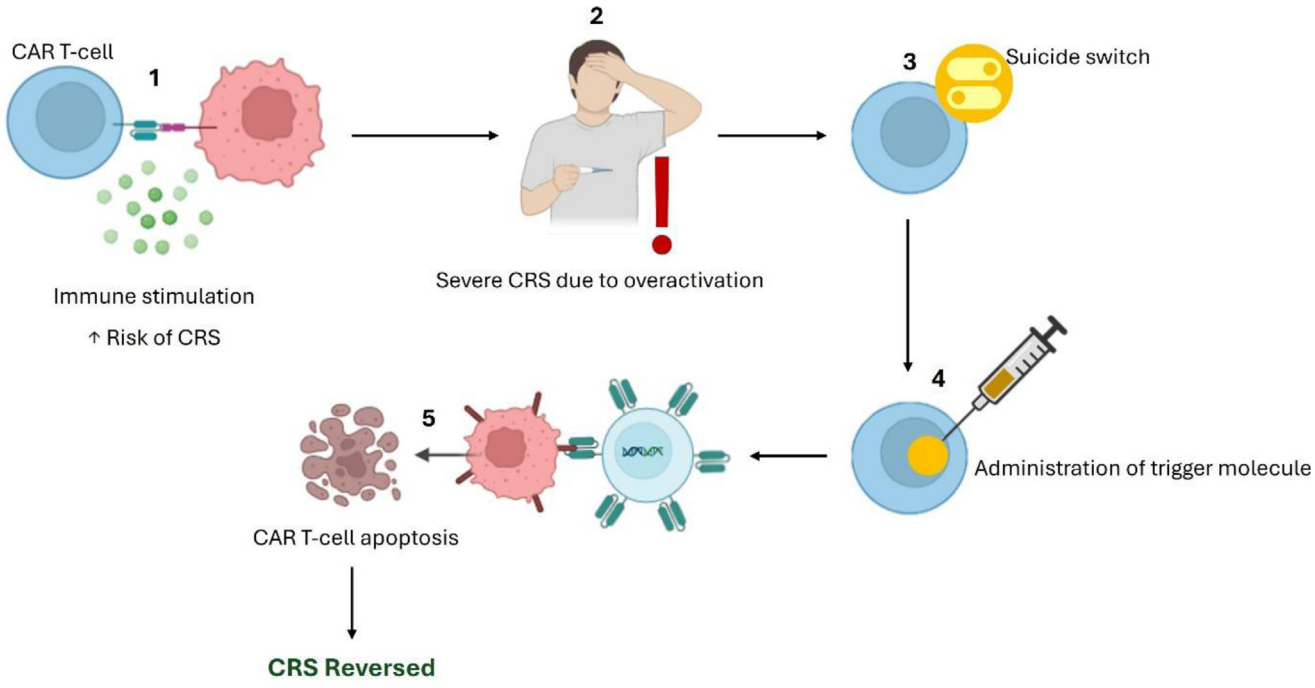

Fig. 2 – Suicide gene switch strategy for managing severe cytokine release syndrome (CRS) in CAR T-cell therapy. (1) CAR T-cell activation – Engineered CAR T-cells recognize and attack tumour cells, leading to cytokine production and immune activation; (2) Onset of severe CRS – Excessive cytokine release results in systemic inflammation and life-threatening CRS symptoms; (3) Suicide gene engineering – CAR T-cells are modified to include a suicide gene switch; (4) Trigger administration – An exogenous small molecule or antibody is administered to activate the suicide switch and (5) CAR T-cell apoptosis and CRS resolution – Triggered CAR T-cells undergo apoptosis, reducing immune activation and reversing CRS (made with Biorender.com).

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(NCT05131763) evaluated the safety and clinical activity of NKG2D-based CAR T-cells infusion in the treatment of relapsed/refractory NKG2DL+ solid tumours but has since been withdrawn [55]. To date, no phase II, III, or IV clinical trials have been registered to determine the clinical benefit of NKG2D CAR T-cells in MB patients.

Although MB data is limited, Weiss et al. demonstrated a preclinical proof-of-concept for NKG2D CAR T-cell activity in mouse glioma models, showcasing efficacy, long-term persistence, and synergistic effects when combined with radiotherapy. These findings support the potential translation of this immunotherapeutic strategy to human glioma patients [56]. In another study, NKG2DLs were detected on U251 cells (human astroglioma) and most glioma patient samples [57]. KD-025 (NKG2D used as an antigen-binding domain to construct a second generation of CAR) expression was more than 50% on T-cell surfaces. Co-incubation of KD-025 CAR T cells with U251 cells significantly increased TNFα, IFN-γ, IL-10, and IL-2 cytokine levels and effectively lysed tumour cells, achieving 50–60% lysis. Remarkably, in their in vivo mouse study, a single treatment with KD-025 CAR T-cells eliminated all tumour cells within 14 days.

However, there is often a risk of antigen escape, particularly NKG2DL escape, which could lead to CAR T-cell resistance and partial evasion of natural killer (NK) cells. Therefore, careful selection of CAR target ligands is crucial to minimize the potential for tumour cell multi-resistance [54].

While the specific outcomes of the above-mentioned CAR T-cell therapies in MB are not yet well established, they have shown promising feasibility in other solid tumours, such as GBM. The results suggest that these CAR T-cell approaches could be considered for inclusion in future clinical trials targeting MB. Table 1 provides a summary of these findings.

7. Limitations: CAR T-cell associated toxicities

Although promising, CAR T-cell therapy can result in treatment-related toxicities, with CRS being one of the most common and severe [58,59]. CRS arises from systemic immune activation, leading to elevated inflammatory cytokines, which typically produce flu-like symptoms. However, severe cases can result in multiorgan system failure and even death. The most elevated cytokines associated with CRS include IL-10, IL-6, and IFN-γ. Management of CRS often involves high-dose corticosteroids and interleukin-6 blockade. More recently, another method to manage severe CRS is engineering suicide genes into the CAR T-cells (Fig. 2). With a suicide gene/switch in place, administration of an antibody or small molecule can induce apoptosis of CAR T-cells to prevent further immune stimulation and reverse CRS [60].

8. Conclusion

Significant advancements over the past decade have facilitated the development of CAR T-cells for brain tumours, specifically MB. Given the variable prognosis for paediatric/adolescent MB, CAR T-cell therapy offers promising potential. However, continued preclinical research is essential to address existing gaps, including optimal delivery methods, microenvironment characterization, target identification, and efficacy enhancement. Despite these challenges, the future of CAR T-cell therapy in managing paediatric/adolescent brain tumours and improving treatment outcomes appears promising. However, financial accessibility remains a significant barrier, as the high costs of development and manufacturing limit availability, particularly in LMICs. Ethical concerns regarding patient selection, affordability, and fair distribution must be addressed to prevent disparities in access. Ensuring distributive justice in CAR T-cell therapy will require frameworks that promote equitable access and affordability, enabling broader implementation across diverse healthcare settings [61].

9. Future reflections

As the field of CAR T-cell therapy continues to evolve, it is important to expand research efforts to address the specific needs of paediatric/adolescent patients. Most studies on CAR T toxicity prevention and management have primarily focused on adult populations, leaving a significant gap in knowledge regarding the unique physiological and pathological characteristics of children and young adults. Given the distinct underlying disease processes and varying tolerance to toxicities in younger patients, it is imperative to conduct comprehensive studies that evaluate acute, delayed, and long-term toxicities associated with CAR T therapy in this demographic.

Future research should prioritize the development of paediatric-specific protocols that not only assess the safety and efficacy of CAR T-cell therapies but also tailor management strategies for toxicities that may differ from those observed in adults. Collaborative efforts among researchers, clinicians, and patient advocacy groups will be essential to foster a better understanding of the implications of CAR T-cell therapy in paediatric populations. By addressing these critical gaps, we can enhance treatment outcomes and improve the overall quality of care for children and young adults receiving CAR T-cell therapy.

Disclosure of interest

The authors declare that they have no competing interest.

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