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Original article

Adoptive immunotherapies in neuro-oncology: classification, recent advances, and translational challenges

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Abstract. *Background:* Adoptive immunotherapies are among the pillars of ongoing biological breakthroughs in neuro-oncology, as their potential applications are tremendously wide. The present literature review comprehensively classified adoptive immunotherapies in neuro-oncology, provides an update, and overviews the main translational challenges of this approach. *Methods:* The PubMed/MEDLINE platform, Medical Subject Heading (MeSH) database, and ClinicalTrials.gov website were the sources. The MeSH terms "Immunotherapy, Adoptive," "Cell- and Tissue-Based Therapy," "Tissue Engineering," and "Cell Engineering" were combined with "Central Nervous System," and "Brain." "Brain tumors" and "adoptive immunotherapy" were used for a further unrestricted search. Only articles published in the last 5 years were selected and further sorted based on the best match and relevance. The search terms "Central Nervous System Tumor," "Malignant Brain Tumor," "Brain Cancer," "Brain Neoplasms," and "Brain Tumor" were used on the ClinicalTrials.gov website. *Results:* A total of 79 relevant articles and 16 trials were selected. T therapies include chimeric antigen receptor T (CAR T) cell therapy and T cell receptor (TCR) transgenic therapy. Natural killer (NK) cell-based therapies are another approach; combinations are also possible. Trials in phase 1 and 2 comprised 69% and 31% of the studies, respectively, 8 of which were concluded. CAR T cell therapy targeting epidermal growth factor receptor variant III (EGFRvIII) was demonstrated to reduce the recurrence rate of glioblastoma after standard-of-care treatment. *Conclusion:* Adoptive immunotherapies can be classified as T, NK, and NKT cell-based. CAR T cell therapy redirected against EGFRvIII has been shown to be the most promising treatment for glioblastoma. Overcoming immune tolerance and immune escape are the main translational challenges in the near future of neuro-oncology. (www.actabiomedica.it)

Key words: Adoptive Immunotherapies, CAR T Cell, Immunotherapy, Malignant Brain Tumor, NK Cell

Background

The rapid development of applied biotechnology in both diagnostics and therapeutics has led to a progressive but dramatic transition in neuro-oncology from an old era, which was purely based on the mechanical, physical or chemical features of conventional surgery, radiotherapy and chemotherapy, respectively, to a new era, which is considered purely biological due to its entirely molecular approach (1). Therefore, the World Health Organization (WHO) has profoundly revised the classification of central nervous system (CNS) tumors, which now involves biomolecular aspects that widely distinguish primitive neoplasms for diagnosis and prognosis of the disease and, especially, the responsiveness to therapy (2). Immunotherapies

are among the main pillars of a biological approach to malignant CNS tumors, with the rationale of enhancement of the neuroimmune response against neoplasms through selective immunomodulation. Immunotherapies of CNS malignancies involve three straightforward strategies: checkpoint inhibitors, vaccines, and adoptive cellular immunotherapies. In contrast to checkpoint inhibitors and vaccines, adoptive immunotherapies necessitate the injection, grafting, or implantation of a cellular product into the patient (3). Thus, adoptive immunotherapies are cell-based therapies, or cytotherapies, which are considered a part of the ongoing biotechnological revolution in neuro-oncology. The concomitant tremendous evolution of translational medicine and nanotechnologies, both propaedeutic to a clinical development in pediatric and adulthood population (4-7), has led to an improvement in bioengineering techniques, which have involved gene therapies more than immunotherapies in the last few years. The spectrum of the potential applications of adoptive immunotherapies is incredibly wide, is not yet thoroughly investigated, and offers a theoretically huge number of possible strategies against CNS and other tumors (8-19).

The aim of the present study was to comprehensively review the literature on the current role of adoptive immunotherapies in neuro-oncology. The future perspectives and challenges of this approach were analyzed in detail.

Methods

An online literature search was conducted with the PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov) platform and the ClinicalTrials.gov (https://clinicaltrials.gov) database, which reports privately and publicly funded clinical studies worldwide. For the MEDLINE search, the Medical Subject Heading (MeSH) database was used.

The MeSH terms "Immunotherapy, Adoptive," "Cell- and Tissue-Based Therapy," "Tissue Engineering," and "Cell Engineering" were selected. For each MeSH term, the search was restricted to specific subheadings (i.e., the classification criteria and clinical employment of adoptive cellular immunotherapies). The aforementioned main terms were combined with further MeSH terms: "Central Nervous System" and "Brain."

A further free text search was conducted using the combination of the terms "brain tumors" [text word] and "adoptive immunotherapy" [MeSH].

Only articles in English or articles translated to English published in the last 5 years and pertinent to neuro-oncology were selected. Review articles and editorials were included, whereas case reports were excluded. An additional sorting was conducted based on the best match and relevance inferred by the titles and abstracts.

On ClinicalTrials.gov, the search terms "Central Nervous System Tumor," "Malignant Brain Tumor," "Brain Cancer," "Brain Neoplasms," and "Brain Tumor" were used. No restrictions for drug name, country, recruitment status, or study phase were applied.

Based on the identifier, duplicated studies were excluded, and only trials regarding adoptive immunotherapies were selected according to the interventions. The retrieved trials were summarized, and the current phase of the studies was highlighted. A descriptive analysis of the most relevant studies from the overall literature search was reported.

Results

1. Literature Volume

The search retrieved 310 articles and 24 clinical trials. After the implementation of the exclusion criteria and removal of duplicates, 79 articles and 16 trials remained.

2. Classification of Adoptive Immunotherapies

Table 1 reports the classification of adoptive immunotherapies for malignant brain tumors.

2.1 Engineered and Activated T cells

Engineered T cell adoptive immunotherapies include chimeric antigen receptor (CAR) T cell therapy and T cell receptor (TCR) transgenic therapy.

Table 1 - Classification of adoptive immunotherapies for malignant brain tumors

Cell	Engineered Effector	
T	TCR transgenic T	
	CAR T (re-directed against)	EGFRIII
		IL-13Ra2
		CD133
		HER2
		EphA2
NK	Allogenic NK	
	Antibody-mediated blocking of KIR	
	Antibodies against EGFR (ADCC)	
	Transplantation of KIR2DS2+ genotype NKs	
	Immunoligands binding NKG2D receptor	
	Cord blood NK cells transduced with (TGF)-β receptor II (DNRII)	
	NKs' exosomes	
	CAR NK targeting EGFR variant III	
NKT	Autologous NKT expanded w/ autologous mature DC loaded with the NKT ligand α-galactosyl ceramide	
Hybrid	Autologous NK + CD8+ cytotoxic T lymphocytes (ALECSAT)	

T: T lymphocyte; NK: natural killer cells; NKT: T lymphocyte-natural killer cells; ALECSAT: Autologuos Lymphoid Effector Cells Specific Against Tumour; CAR T: chimeric antigen receptor; EGFRIII: epidermal growth factor receptor variant III; IL-13Ra2: interleukin-13 receptor α2; CD: cluster differentiation; HER2: human epidermal growth factor 2; EphA2: erythropoietin-producing hepatocellular carcinoma A2; EGFR: epidermal growth factor receptor; ADCC: antibody-dependent cellular cytotoxicity; KIR2DS2: killer cell immunoglobulin like receptor, two Ig domains and short cytoplasmic tail 2; TGF: transforming growth factor; DNRII: dominant-negative receptor II; CTL: cytotoxic T-lymphocytes.

2.1.1 CAR T Cells

CAR T cell therapy is based on an ex vivo expansion of leukocytes, and the engineering of these cells aims to form a chimeric receptor powered by selectivity for neoplastic targets, which is several orders of factors higher than its naïve form, and the autologous or allogenic transplant.

Interleukin 2 and anti-CD3 antibodies and gamma-retroviruses and lentiviruses are used for the activation and proliferation of T cells and transfection of CAR genes, respectively (20).

The oncolytic capability of these cells, as well as their proficiency to overcome immune tolerance, lies in the chimeric nature of CAR, which involves single receptor antigen-binding and T-cell activating properties. CAR T cells are redirected against a specific protein expressed on neoplastic cell membranes, and the neoplastic cells are thus selectively killed (21, 22). Consequently, the specificity of CAR T cells for a specific type of tumor largely depends on the types of transfected CAR genes. Adoptive immunotherapy for malignant brain tumors, and primarily glioblastoma, has tested several CAR genes, namely, epidermal growth factor receptor variant III (EGFRvIII) (23-25), interleukin-13 receptor a2 (IL-13Ra2) (26-29), CD133 (26), human epidermal growth factor receptor 2 (HER2) (30, 31), and erythropoietin-producing hepatocellular carcinoma A2 (EphA2) (32). Lymphodepletion prior to adoptive transfer of tumor-specific CAR T lymphocytes has been reported to be among the key factors enhancing the expansion and efficacy of the transplant, mainly by means of the abolishment of regulatory T cell activity and competing elements of the immune system (cytokine sinks) (33-35).

2.1.2 TCR Transgenic T Cells

TCR transgenic T cell therapy involves the isolation of the α and β chains of the TCR, with the latter binding the major histocompatibility complex (MHC) on the cellular membrane, their manipulation_aimed to enhance the selectivity and specificity for specific tumoral antigens, their insertion into retroviruses or lentiviruses, the amplification of the viral vectors and, patient infection (36-38).

2.2 Natural Killer (NK) Cells

The spectrum of the possible molecular mechanisms of NK cell-mediated adoptive immunotherapy is highly variable.

2.2.1 Allogenic NK Cell Transplant

The rationale of allogenic NK cell transplant lies in the inability of these cells to recognize MHC class I molecules and human leukocyte-antigen (HLA) type A ligands expressed by glioma cells, which ultimately enhances the oncolytic effect. Transplantation of the cells belonging to the immune system has been reported to be less affected by the risk of rejection than other allogenic transplants, and this concept is the backbone of allogenic immunotherapies (39).

2.2.2 NK Killer Immunoglobulin-Like Receptor (KIR) Antibody-Mediated Blocking

Antibody-mediated blocking of inhibitory cell KIRs has been associated with a dramatic increase in NK-mediated killing of neoplastic cells, mainly due to the inhibition of the well-known negative regulatory properties of this receptor of the NK cell function (40).

2.2.3 Antibody-Dependent Cellular Cytotoxicity (ADCC)

ADCC has been employed to treat glioblastoma and classically uses EGFR antibodies. The fragment crystallizable (FC) region of the antibody binds some activating receptors expressed by NK cells, ultimately leading to cancer cell apoptosis. CD16 (FcγIIIA), KIR two domains, short cytoplasmic tail, 2 (KIR2DS2), and NK Group 2D (NKG2D) are the most studied among these receptors. The KIR2DS2+ genotype has been reported to have the greatest cytotoxicity and non-negligible inhibition of angiogenesis in experimental models (41).

2.2.4 NK Cell Immunoligands

Immunoligands able to selectively bind NKG2D receptors have also been tested (41).

2.2.5 Retrovirally Transduced Cord Blood NK Cells

Yvon et al emphasized the properties of cord blood-derived NK cells retrovirally transduced to express a dominant negative form of transforming growth factor (TGF)-β receptor II (DNRII) specifically for gliobastoma (42). DNRII makes these cells immune to the detrimental effects of TGF-β produced by the microenvironment and causes immune escape of the glioma cells.

2.2.6 NK Cell Exosome Mimetics

Evidence of the efficacy of NK cell exosome mimetics against malignant brain tumors was derived from in vitro and in vivo studies. NK cell exosomes are endogenous nanocarriers that can enhance the biological activity of NK cells against tumors.

2.2.7 CAR NK Cells

The CAR NK cell line targeting EGFRvIII was produced according to the aforementioned mechanisms described for CAR T cells and has been successfully employed for glioblastoma (43).

Regardless of the type of approach used, NK cell adoptive immunotherapy for glioblastoma has been combined with the mAb9.2.27 antibody, which is able to inhibit angiogenesis through the secretion of interferon (IFN)-γ and tumor necrosis factor (TNF)-α (44, 45).

Figure 3 displays an overview of the main molecular mechanisms involved in NK cell-based immunotherapy for glioblastoma.

2.2.8 NKT Cells

CD1d-restricted NKT cells have been reported to have a fundamental role in both the innate and acquired immune responses against tumors. Differences do exist among CD1d-restricted NKT cells between type I and type II, which have invariant Valpha14 and heterogeneous non-Valpha14 receptors, respectively (46).

The immunological escape of malignant CNS tumors from NKT cells occurs through the high level of expression of microRNA-92a and an immune tolerant IL-6+ IL-10+ NKT cell phenotype (47-50). An approach aimed to overcome the immune tolerance of glioma cells includes the expansion in culture of NKT cells using autologous mature dendritic cells (DCs) loaded with the NKT ligand α-galactosyl ceramide, which effectively stimulates murine and human type I NKT cells (46, 51-53).

2.3 Hybrid Therapies

Autologous Lymphoid Effector Cells Specific Against Tumor cells (ALECSAT) therapy (Cytovac A/S, Hørsholm, Denmark) is an epigenetic, thus not involving DNA manipulation, cancer adoptive immunotherapy under investigation for glioblastoma and prostate and pancreatic cancer. The main steps of ALECSAT therapy entail the following distinct phases: isolation of lymphocytes and monocytes from the patient's peripheral blood sample; culture and differentiation of monocytes into DCs; co-culture of mature DCs and lymphocytes to create autologous activated T helper (Th) cells; induction of CD4+ Th cells with 5-aza-2′-deoxycytidine, a DNA-demethylation agent, to express cancer/testis antigens (CTA-Th); addiction of CTA-Th cells to non-activated lymphocytes to obtain activated and expanded CD8+ cytotoxic lymphocyte (CTL) effectors; and injection of autologous NK and CD8+ CTL effectors (54). Activated NK cells are directed against glioma cells that do not express the antigen. The ALECSAT immunization protocol lasts 26 days. Strengths of this approach are the population of secondary lymphoid organs for a long-lasting effect and the wide variety of tumor antigens.

3. Clinical Trials on Adoptive Immunotherapies

Out of 16 clinical trials, 69% were phase 1, and 31% were phase 2 (Figure 1). Most of them are still ongoing in the USA and China (56% and 25%, respectively) (Figure 2). Only 8 of these studies have been concluded. Three involved ALECSAT immunotherapy. The first two ALECSAT trials (NCT02799238 and NCT01588769) aimed to evaluate the tolerability and efficacy of this therapy, whereas the third trial (NCT02060955) compared its efficacy to bevacizumab plus irinotecan. To date, no results have been released for any of these trials. A phase 2 completed study on CAR T cell receptor immunotherapy targeting EGFRvIII for patients with malignant gliomas expressing EGFRvIII (NCT01454596) concluded that this approach effectively and safely reduces the recurrence rate of glioblastoma after standard-of-care treatment, specifically by means of the elimination of

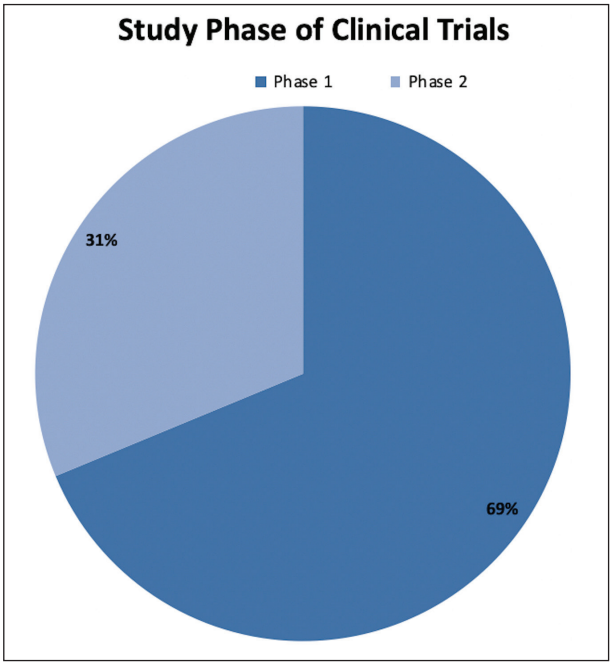

Figure 1. Pie graph showing the distribution of the clinical trials according to the study phase

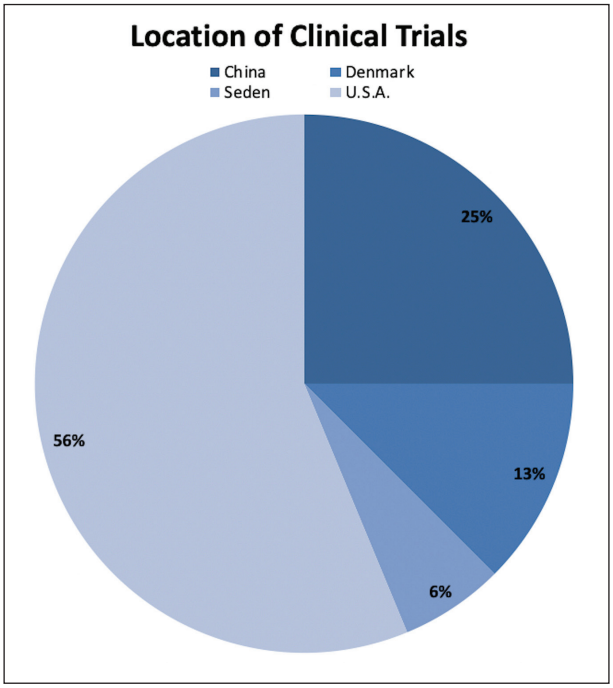

Figure 2. Pie graph showing the distribution of the selected clinical trials according to study location

glioma stem cells (55). The remaining completed trials tested the efficacy of alloreactive CD8+ cytotoxic T lymphocytes or the combination of adoptive T cell-based immunotherapy with other immunomodulators, such as aldesleukin, a lymphokine produced through recombinant DNA technology using a genetically engineered *E. coli* strain containing an analog of the human interleukin 2 gene (56-60). Positive results were reported for some of these combinations. Table 2 summarizes the clinical trials on adoptive immunotherapies for malignant gliomas.

Discussion

Recently, neuro-oncology has experienced a landmark transition from a mechanical era to a biological era (61-63).

A concrete aspect of this evolution is the last WHO classification of CNS tumors, which originated from the advances in genomic profiling and proteomics (64) and led to an improvement in their overall management in terms of diagnosis, prognosis, and, especially, adjuvant therapy.

Despite the refinements in neurosurgical techniques in neuro-oncology and other fields (65-73), the progression free survival and the overall survival for patients with high grade gliomas remain dismal. This aspect has justified the compulsive search of adjunctive biological therapies based on the new insights in neuroimmunology.

Theoretical application of adoptive immunotherapies and implementation of clinical trials have been possible due to the tremendous advances in somatic cell biotechnologies (74). These technologies involve manipulation of the allogenic or xenogeneic immunological cells to obtain a cellular product that is transplanted as a living drug. A straightforward and practical classification of adoptive immunotherapy is shown in Table 1 and is essentially based on the immunophenotype of the cellular product. A classification scheme like this has a strength mainly in pursuing a modular approach of biological immunotherapy, often involving the combination of different immunophenotypes with a subsequent potential synergic effect. The overall level of evidence of the efficacy of adoptive immunotherapies in neuro-oncology is remarkably promising but remains insufficient to be considered immediately applicable in daily clinical practice. Most of the trials are in phase 1, and most of those in phase 2 remain ongoing or incomplete. CAR T cell therapy has a valuable rationale for brain cancer, and this rationale is likely the main reason why this approach has fostered much attention. An addition reason is the tremendously positive results of this approach in hematology and other fields, where CAR T cell therapy accounts for more than 25 years of cumulative experience (75-77). In glioblastoma adjuvant therapy, CAR T cells redirected against EGFRvIII have especially shown positive results (23-25, 55). ALECSAT immunotherapy also has received much attention, even though no consistent data have been reported apart from a good safety profile (54).

Most adoptive immunotherapies involve therapeutic depletion of regulatory T cells (Tregs), as an immunomodulatory approach, based upon the assumption that both thymus-derived and inducible therapies that play a role are involved in the immune tolerance of glioblastoma (78, 79).

Adoptive immunotherapies for malignant brain tumors face a non-negligible number of translational challenges, almost all of which converge toward the need to overcome the immunological tolerance of glioma and the immune escape of glioma stem cells. Several factors are responsible for the immune tolerance of glioma cells, which are primarily the lack of tumor antigen expression and the subsequent loss of the tumor immunological phenotype. This aspect is deleterious for the success of both T-cell based and vaccine immunotherapy. Thus, aberrant nitric oxide synthase 2 is gaining more interest as a further potential therapeutic target. For TCR therapy, the main limiting factor is the mispairing between endogenous α/β and transgenic α/β TCR chains, and no clinical trials have been established for malignant brain tumors (38, 80). An NK cell-based approach recognizes that the lack of the representativeness of these cells within the tumor microenviroment is its main limitation (81). The main reason for this limitation seems to be the high representativeness of the MHC class I molecules and of the HLA ligand type A on glioma cells. Both of these molecules can interact with inhibitory NK cells

Table 2. Clinical Trials on Adoptive Immunotherapies for Malignant Brain Gliomas

#	ClinicalTrials.gov Identifier	Condition or Disease	# of Pts. Estimated Enrollment	Intervention/Treatment	Study Arms	Study Phase	Recruitment Status	Locations
1	NCT03392545	High Grade Glioma; Glioblastoma Glioma of Brainstem Glioma, Malignant	30	Combined immune adjuvants and radiation	Combination of Immunization and Radiotherapy for Recurrent GBM (InSituVac1)	1	Recruiting	CH
2	NCT03389230	Glioblastoma HER2/Neu Positive Malignant Glioma Recurrent Glioma Refractory Glioma WHO Grade III Glioma	42	HER2(EQ)BBζ/CD19t+ Tcm	Memory-Enriched T Cells in Treating Patients with Recurrent or Refractory Grade III-IV Glioma	1	Recruiting	U.S.
3	NCT03347097	Glioblastoma Multiforme	40	TIL	Tumor-infiltrating T Lymphocyte (TIL) Adoptive Therapy for Patients with Glioblastoma Multiforme	1	Recruiting	CH
4	NCT03344250	Glioblastoma Glioblastoma Multiforme	18	EGFR BATs with SOC RT and TMZ	Phase I EGFR BATs in Newly Diagnosed Glioblastoma	1	Recruiting	U.S.
5	NCT03170141	Glioblastoma Multiforme of Brain Glioblastoma Multiforme	20	Antigen-specific IgT cells	Immunogene-modified T (IgT) Cells Against Glioblastoma Multiforme	1	Enrolling by invitation	CH
6	NCT02937844	Glioblastoma Multiforme	20	Anti-PD-L1 CSR T cells	Pilot Study of Autologous Chimeric Switch Receptor Modified T Cells in Recurrent Glioblastoma Multiforme	1	Recruiting	CH

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Table 2. Clinical Trials on Adoptive Immunotherapies for Malignant Brain Gliomas

#	ClinicalTrials.gov Identifier	Condition or Disease	# of Pts. Estimated Enrollment	Intervention/Treatment	Study Arms	Study Phase	Recruitment Status	Locations
7	NCT02799238	Glioblastoma	62	ALECSAT	Autologuos Lymphoid Effector Cells Specific Against Tumour (ALECSAT) as Add on to Standard of Care in Patients with Glioblastoma	2	Active, not recruiting	SW
8	NCT02208362	Malignant Glioma Refractory Brain Neoplasm Recurrent Brain Neoplasm Glioblastoma	92	IL13Rα2-specific, hinge-optimized, 41BB-costimulatory CAR/truncated CD19-expressing Autologous T lymphocytes, Vaccine Therapy	Genetically Modified T-cells in Treating Patients with Recurrent or Refractory Malignant Glioma	1	Recruiting	U.S.
9	NCT02060955	Glioblastoma Multiforme	25	ALECSAT	Randomized Phase 2 Study to Investigate Efficacy of ALECSAT in Patients with GBM Measured Compared to Avastin/Irinotecan	2	Completed	DE
10	NCT01588769	Glioblastoma Multiforme	23	Anti-EGFRvIII CAR transduced PBL	A Phase I Study to Investigate Tolerability and Efficacy of ALECSAT Administered to Glioblastoma Multiforme Patients (ALECSAT-GBM)	1	Completed	DE
11	NCT01454596	Malignant Glioma Glioblastoma Brain Cancer Gliosarcoma	18	Anti-EGFRvIII CAR Transduced PBL	CAR T Cell Receptor Immunotherapy Targeting EGFRvIII for Patients with Malignant Gliomas Expressing EGFRvIII	2	Completed	U.S.

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Table 2. Clinical Trials on Adoptive Immunotherapies for Malignant Brain Gliomas

#	ClinicalTrials.gov Identifier	Condition or Disease	# of Pts. Estimated Enrollment	Intervention/Treatment	Study Arms	Study Phase	Recruitment Status	Locations
12	NCT01144247	Gliomas Anaplastic Astrocytoma Anaplastic Oligodendroglioma Anaplastic Mixed Glioma Glioblastoma Multiforme Malignant Meningioma	10	Alloreactive CTL	Cellular Immunotherapy Study for Brain Cancer	1	Completed	U.S.
13	NCT01082926	Anaplastic Astrocytoma Anaplastic Ependymoma Anaplastic Meningioma Anaplastic Oligodendroglioma Brain Stem Glioma Ependymoblastoma Giant Cell Glioblastoma Glioblastoma Gliosarcoma Grade III Meningioma Meningeal Hemangiopericytoma Mixed Glioma Pineal Gland Astrocytoma Brain Tumor	6	Therapeutic allogeneic lymphocytes - aldesleukin	Phase I Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Intratumoral Infusions of GRm13Z40-2, An Allogeneic CD8+ Cytolitic T-Cell Line Genetically Modified to Express the IL 13-Zetakine and HyTK and to be Resistant to Glucocorticoids, in Combination with Interleukin-2	1	Completed	U.S.

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Table 2. Clinical Trials on Adoptive Immunotherapies for Malignant Brain Gliomas

#	ClinicalTrials.gov Identifier	Condition or Disease	# of Pts. Estimated Enrollment	Intervention/Treatment	Study Arms	Study Phase	Recruitment Status	Locations
14	NCT00730613	Brain and Central Nervous System Tumors	3	Biological: therapeutic autologous lymphocytes	Cellular Adoptive Immunotherapy Using Genetically Modified T-Lymphocytes in Treating Patients with Recurrent or Refractory High-Grade Malignant Glioma	1	Completed	U.S.
15	NCT00331526	Brain and Central Nervous System Tumors	83	Aldesleukin	Cellular Adoptive Immunotherapy in Treating Patients with Glioblastoma Multiforme	2	Completed	U.S.
16	NCT00004024	Brain and Central Nervous System Tumors	60	Aldesleukin, autologous tumor cell vaccine, muromonab-CD3, sargramostim, therapeutic autologous lymphocytes	Biological Therapy Following Surgery and Radiation Therapy in Treating Patients with Primary or Recurrent Astrocytoma or Oligodendroglioma	2	Completed	U.S.

HER2(EQ)BBζ/CD19t+ Tcm: preparation of genetically modified autologous central memory enriched T-cells (Tcm) expressing a chimeric antigen receptor consisting of an anti-human epidermal growth factor 2 (HER2) variable fragment that is linked to the signaling domain of the T-cell antigen receptor complex zeta chain (BBζ), and truncated cluster of differentiation (CD)19; **TIL**: Tumor-infiltrating T-Lymphocyte; **EGFR**: epidermal growth factor; **EGFRvIII:** epidermal growth factor receptor variant III; **EGFR BATs:** EGFR Bi-armed Activated T-cells; **RT:** radiotherapy**; TMZ**: temozolomide; **PD-L1 CSR**: programmed death Ligand 1 chimeric switch receptor; **IL-13Rα2**: interleukin-13 receptor α2; **ALECSAT**: Autologuos Lymphoid Effector Cells Specific Against Tumour; **PBL**: peripheral blood lymphocytes; **CTL**: cytotoxic T-lymphocytes; **GBM**: glioblastoma; **CH:** China; **U.S.**: United States; **SW:** Sweden; **DE:** Denmark.

and KIRs, ultimately inhibiting the functions of NK cells (40).

Similar challenges are related to adoptive immunotherapies for other solid tumors (82).

A further consideration for adoptive immunotherapies, which are somatic cell-based therapies, is their susceptibility to genetic and phenotypic modifications with a subsequent dramatic decrease in their biological activity as a consequence of extensive tissue culture expansion (83).

Conclusion

Adoptive immunotherapies can be classified based on the immunophenotype of the cellular product. They involve treatments based on T, NK, and NKT cells, along with hybrid approaches from their combination.

CAR T cells redirected against EGFRvIII have shown positive results in the treatment of recurrent glioblastoma. Different NK cell-based approaches are also being considered, ranging from allogenic transplant to exosomes mimetics, each with different potential.

The comprehensive level of evidence for the efficacy and safety of adoptive immunotherapies in neuro-oncology is non-negligible but remains insufficient to consider these therapies as a standard of care.

Constant immune tolerance and immune escape by high grade gliomas are the main limiting factors of these therapies, and they are among the most important translational challenges for the near future of neuro-oncology.

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