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Emerging Innovations in Cancer Immunotherapy

The quest for GBM treatment ends with Personalized Immunotherapy: *A Promising Game Changer*

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Latest News

Collaboration between APAC Biotech and AIIMS, India

On the basis of the clinical outcomes, APAC Biotech has managed to sign an official agreement with All Indian Institute of Medical Sciences (AIIMS, located in Delhi, INDIA) to conduct first ever Phase II trial investigating safety and efficacy of DC based immunotherapy among newly diagnosed GBM patients in India. Unlike Northwest Biotherapeutics, a dual antigen loading strategy (tumor lysate + tumor mRNA) will be employed to prepare DC based immunotherapy. Our final product, named LTR-MEMVAXRALEUCEL (**LTR-M**) will be administered biweekly as perinodal and intradermal infusion to 120 enrolled patients following completion of conventional treatment regime as per Stupp protocol.

This open label, multi-centre, randomized, double arm study will be completed in 3 years of time during which overall survival and quality of life will be assessed from the date of initiation of therapy to the date of death among treated and control groups.

Glioblastoma Multiforme (GBM) constitutes the most common and lethal WHO grade IV diffuse glioma. Although GBM is surgically incurable in vast majority of patients, management of newly diagnosed GBM includes maximal tumor resection followed by combined concurrent chemo-radiation and adjuvant **Temozolomide** (TMZ) therapy as outlined by Stupp *et.al.*

The median survival duration for patients with GBM is only 9–15 months

Despite advances in standard therapy, the prognosis for patients with GBM remains poor. The **blood-brain barrier** (BBB) is a major impediment to intracerebral difusion of drugs used to treat brain cancer, reducing the efficacy of therapeutic drugs by preventing them from penetrating into the brain. In several cases, often treatment of GBM fails as majority of tumors are MGMT unmethylated because of which they are highly resistant to conventional cytotoxic chemotherapy and RT. Furthermore, the glioblastoma microenvironment is a **highly immunosuppressive** milieu of tumour cells and immune cells. Tumour cells express increased levels of immunosuppressive factors such as TGFβ, IL-10, programmed cell death ligand 1and indolamine 2,3-dioxygenase which down regulates the local myeloid and lymphoid immune cells and promotes systemic immunosuppression. Thus, **conventional therapy succeeds only in controlling the disease, not eradicating it**. Moreover, prolonged radiotherapy induces damage to the normal neural tissue, which may lead to clinically significant deterioration in cerebral function.

Regardless of modern treatments and diagnosis techniques, the median survival duration for patients with GBM is only 9–15 months, and majority die within 2 years. Only 5% patients are able to show survival of 5 years approximately. The significant clinical need for effective treatments of brain tumor has raised efforts to induce active immune surveillance against glioma cells in the brain by strengthening the adaptive arm of the immune system, predominantly by vaccination, have been pursued as a promising path forward.

Citation	Study type	Case	DC-vaccine treated	Antigen source	Culture of DC	Dosage	Immunological reaction	Clinical response
[2]	Case report	1	R-GBM	allogeneic MHC-I GBM peptides	GM-CSF and IL-4;	I.d. ½ wks (X 3)	Increased TILs	PD, OS:21m
[4]	Phase I	9	N-GBM(n=7), AA(n=2)	autologous tumor specific, MHC-I	GM-CSF and IL-4;	s.c. ½ wks (X 3)	SCR, TILs (CTL and Tm)	Med OS; 455d
[3]	Phase I	8	GBM(n=5), AA(n=3)	ATC	GM-CSF, IL-4 and TNF-α	I.d. 1/3 wks (X 9)	Increased NK cells, IFN-γ	PR(n=2); SD(n=4); PD(n=2);
[6]	Phase I/II	10	GBM(n=7), AA(n=3)	ATL	GM-CSF and IL-4	I.d. and/or I.t. (ommaya) 1/3 wks (X 10)	Increased NK cells; DTH+; Infiltration of T cells	–
[5]	Phase I/II	17	N-GBM, R-GBM	ATL	GM-CSF and IL-4; 3	s.c.,1/2 wks (X 3)+1 at 6th wks	Increased IFN-γ	–
[11]	Phase I/II	14	N-GBM(n=1) and AA (n=1); R-GBM(n=9) and AA(n=3)	ATL	CM-CSF and IL-4	s.c. 1 /2 wks (X 3)	Increased IFN-γ mRNA	Med OS; 133 wks
[7]	Phase I	7	EM (n=3); GBM(N=2); AA(n=1); PA(n=1); MB(n=1); PXAs (n=1)	Tumor tissue RNA	GM-CSF and IL-4	I.v. and I.d. ½ wks X 2+1/1 mth (X 5)	-	-
[9]	Case report	1	AA	ATL	GM-CSF and IL-4; TNF-α, IL-1β, and PGE2	I.d. ½ wks (X 2)+1/1 mth (X 6)	DTH(+)	PFS(60m)
[8]	Phase I	12	HGG (n=8), AA(n=4)	ATL	GM-CSF and IL-4; TNF-α, IL-1β, and PGE2	I.d. 1 at 1st w+2 at 2nd+1/1 mth	DTH(+)	CCR(1), NC(3), PD(3); Med OS: 42.0 wks
[10]	Phase I/II	15	GBM(n=6); AA(n=9)	ATC	FCs and rhIL-12 GM-CSF, IL-4, and TNF-α;	I.d , s.c. ½ wks (X 6)	Increased IFN-γ.	PR (1), MR(1), NC (1), PD(3)
[13]	Phase I	12	N-GBM(n=7); R-GBM(n=5)	Acid-eluted ATCP	GM-CSF and IL-4	I.d. 1/2-4 wks (X 3)	Tumor specific CTL;	Med PFS: 15.5 m Med OS: 23.4 m
[12]	Phase/ II	24	R-AA(n=6); GBM(n=18)	ATL	GM-CSF and IL-4; OK-432	I.d. or I.d. combined I.t. (ommaya) 1/3 wks	DTH(+); Increased tumor specific CTLs	Med OS 480d; PR(1), MR(3), NC(6), PD(8)
[14]	Phase I	7	R-GBM ; AA	Irradiated ATC and TFG-IL4-Neo-TK-transfected fibroblast	UPCI95-033 UPCI 99-111	I.d. 1 st in D1+2nd in D7 +1/2 wks	CD4+, CD8+ IFN-γ against EphA2883–89; HLA-A2	UPCI95033: Stable disease 4m (n=2) UPCI99-111: Med PFS 6m
[16]	Phase II	34	N-GBM(n=11); R-GBM(n=23)	ATL	GM-CSF and IL-4	s.c. ½ wks (X 3)+1st wk#6	Increased IFN-γ	N-GBM OS: 642 ± 61d; PFS: 308 ± 55d; R-GBM OS: 599 ± 75d; PFS: 401 ± 53d
[24]	Phase I	13	GBM(n=9) and AA(n=4)	ATC	GM-CSF and IL-4	I.d. ½ wks (X 6)+1/6 wks	Increased T cell infiltration	Med OS: 11m
[15]	Phase/ II	56	R-GBM	ATL	GM-CSF and IL-4; TNF-α, IL-1β, and PGE2	I.d. G1: 1st, 1w, 2nd, 3 w, ¼ wks; G2: ½ wks (X 5), ¼ w; G3: 1/1 w (X 4)	DTH(+)	Med PFS 3m; OS, 9.6m.
[17]	Phase/ II	45	HGG(n=33), MB/ PNET(n=5), EM(n=4) and ATRT(n=3)	ATL	GM-CSF and IL-4	I.d. G1: 1st, 1 w, 2nd, 3 w, ¼ w; G2: ½ w (X 5), ¼ w; G3: 1/1 w (X 4), ATL; G4: 1/1 w (X 4)	-	HGG: Med OS 13.5m
[18]	Phase/ II	8	N-GBM	ATL	GM-CSF and IL-4; TNF-α, IL-1β, and PGE2	I.d. 1/1 w (X 4)+1/2 wks (vacc+ATL)	Increased CD8+CD25+cell, T-cell IFN-γ	Med OS: 24m; PFS: 18m
[19]	Phase I/II	17	N-GBM, AA and R-GBM, AA	ATL	INF-Y	S.C 1/1wks (X 4)+1/2 wks (X 2)+1/2 mth (X 4)	Increased TIL	GBM:Med:OS 520d
[42]	Phase I	5	R-HGG	Stem-like associate antigen	GM-CSF and IL-4	½ w (X 3)+poly–ICICI M1/2 wks	-	-
[21]	RCT Phase II	34	N- GBM and R- GBM	ATL	GM-CSF and IL-4	s.c. 1/1 w (X 4)+½ wks (X 2) +1/4 wks (X 4)	-	Med OS: 31.9m; Med PFS: 8.5m
[22]	Phase II	25	N-and R- GBM	ATC antigen by heat-shock	GM-CSF and IL-4	I.d. 1st in D7+2nd in D14+3rd in D28+4th in D42	-	Med OS: 17 m
[23]	Phase I	34	GBM(27) and AA(7)	ATL, GAA	GM-CSF and IL-4	½ wks+1/3 mth	Lymphocyte subset change	ATL/GAA; Med OS 34.4m/15.5m

Table 1: Characteristics of clinical trials against gliomas using DCs based vaccine

Immunotherapeutic Strategies for treating GBM

The field of innovative immunotherapeutic approaches to treat glioblastoma is rapidly expanding. Despite the relative paucity of data on active immunotherapies in humans with glioblastoma, more than 70 clinical trials involving the use of immunotherapy for glioblastoma have been completed (Table 1). Among them, three immunotherapeutic approaches have reached phase III clinical development, and numerous others are at earlier stages of clinical testing.

DC based personalized Immunotherapy

Dendritic cells are master Immune cells; and highly potent APCs

Since Dendritic cells (DCs) can activate up to 5000 T cells per hour, they are considered the most powerful antigen presenting cells and thus DC-based vaccination has the potential to target and eliminate GBM cells and enhance the responses of these cells to the existing therapies with minimal damage to the healthy tissues around them. It can also **enhance recognition** of GBM cells by the patient's immune system and activate vast, potent, and long-lasting immune reactions to eliminate them. DC based immunotherapy relies on DC-mediated presentation of glioblastoma associated peptides, antigens, or epitopes derived from tumour lysates to T cells of the adaptive immune system through MHC class II–T cell receptor (TCR) (signal 1) and CD80 and/or CD86–CD28 (signal 2) interactions. The cytotoxic T lymphocytes (CTLs) that are subsequently activated interrogate and destroy tumour cells containing glioblastoma- associated antigens presented on MHC class I molecules (**Figure 2**). Therefore, this therapy can prolong the survival of GBM patients and has great potential in treatment of GBM.

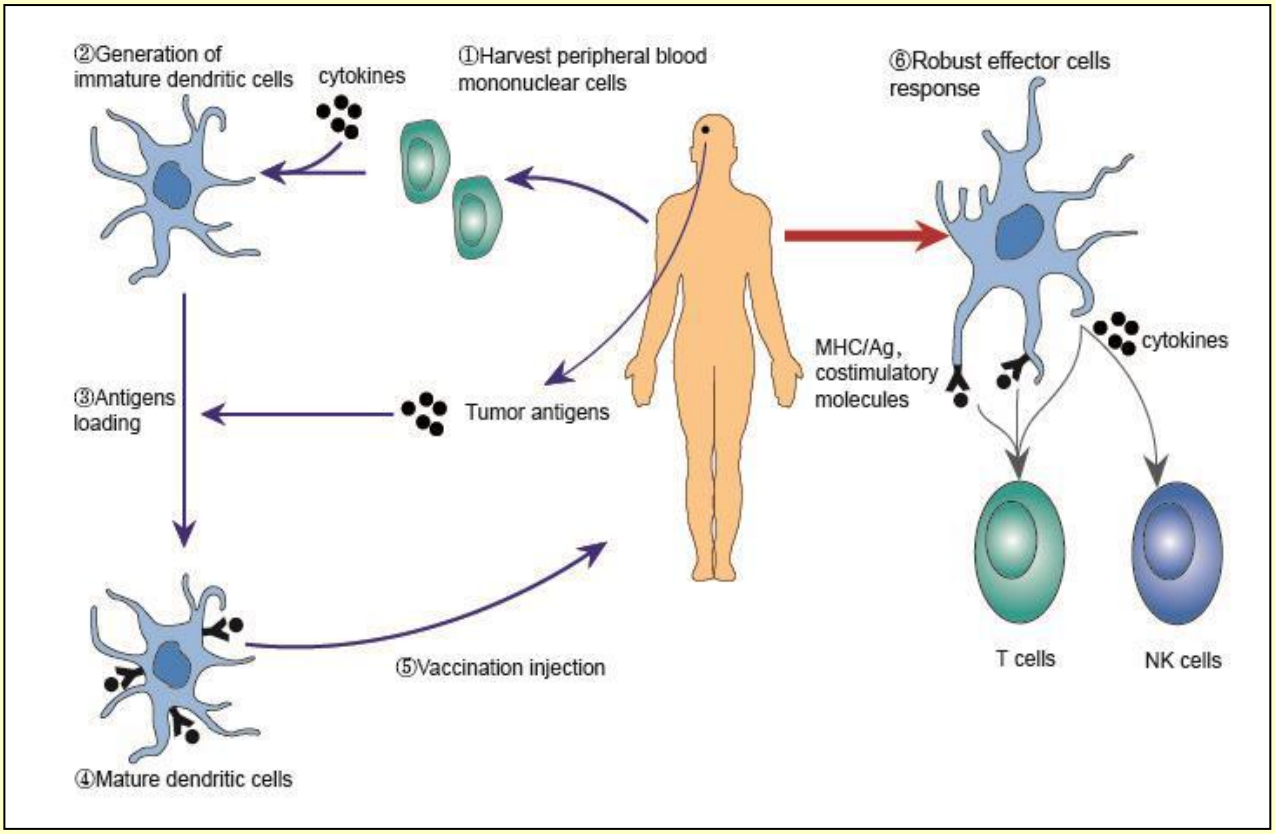

Figure 2: DC-based immunotherapeutic strategies: (1) to harvest peripheral blood mononuclear cells, (2) to generate immature DCs with cytokine stimulation, (3) to mature DCs by loading tumor antigens, (4) to transfer activated antigen-presenting DCs back to the patients, (5) to stimulate robust anti-tumor immune effector cells such as T cells and NK cells.

Since 2018, **33** Phase I & II trials have investigated the safety and efficacy of DC based immunotherapy on patients diagnosed with GBM. Recently a NIH funded Phase III trial was performed by Northwest Biotherapeutics to evaluate safety and survival time among 349 patients with GBM following treatment with DCVAX-L. The therapy involved the use of patient's tumor lysate along with PBMC's from which DC's were isolated. The cells were pulsed with tumor lysate prior to administration into patient's system. The therapy

was labeled safe and showed median overall survival of 23.1 months from surgery. DCVax-L was administered by intra-dermal injection in the arm, six times in year one and twice per year thereafter. The rate of total adverse events with SOC (standard of care treatment) plus DCVax-L was comparable to SOC alone

Recent Advancements in DC Immunotherapy

Several preclinical studies have demonstrated the safety and efficacy of DC based immunotherapy along with an enhanced survival benefit among cancer subjects. A Phase I trial was also conducted by ***Baylor College of Medicine*** on canine patients diagnosed with oligodendroglioma. A dual loading approach was involved in this study where autologous DCs were **doubly** loaded with tumor antigen lysate as well as mRNA fractions and injected bilaterally into near vicinity of deep cervical lymph nodes by means of ultrasound sonography. Dr William Decker and his team demonstrated that administration of DC therapy following conservative surgical resection of tumor induced significant tumor shrinkage. The doubly-loaded DC vaccination was feasible, safe and could mediate tumor regression, and extended life from 68-200 days. Moreover, double loaded DC therapy plus 5'-azacitidine and imiquimod in canine diagnosed with high grade glioblastoma prevented death in 70% 0f inoculated animal compared to animals treated with each therapy individually.