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Adoptive T Cell Therapies for Glioblastoma

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Abstract

Glioblastomas (GB) are the most common primary tumors of the brain. GB are highly invasive and shows a high degree of cellular and genetic heterogeneity. Unfortunately, the biological and genetic properties of GB hinder the ability of conventional therapies to completely eradicate these tumors. To improve patient survival, researchers have devised multiple therapeutic strategies that take advantage of the inherent ability of immune cells to initiate powerful anti-tumor immune responses. Amongst the various forms of immunotherapy for brain tumors, adoptive T cell therapy (ATCT) involves the direct transfer of *ex vivo* activated and tumor-specific T lymphocytes to tumor patients. One advantage of ATCT is that the transfer of tumor-reactive T cells allows for rapid tumor targeting that minimizes the deployment of tumor immune evasion mechanisms. New technological breakthroughs such as the ability to genetically engineer T cells with T cell receptors and chimeric antigen receptors (CAR) against shared tumor antigens have sparked new interest and enthusiasm for ATCT. Here, the different ATCT approaches that have been developed and tested for GB are discussed.

Keywords: Glioblastoma; Adoptive T cell therapy; Chimeric antigen receptors; T lymphocytes

Introduction

Glioblastomas (GB) are the most common primary tumors of the central nervous system (CNS) [1,2] comprising approximately 70% of all primary CNS tumors. Histologically, GB show a high degree of morphologic heterogeneity, microvascular proliferation and necrosis [3] and they are postulated to arise from transformed glial or neural stem cells [1-4]. In 1940, the German pathologist Hans-Joachim Scherer was the first to distinguish primary and secondary GB on the basis of their mode of evolution [5]. He postulated that the progression of lower grade astrocytomas to GB was responsible for GB of long clinical duration. It is now well established that secondary GB develop by progression from less malignant astrocytomas and these tumors occur in relatively younger patients [6]. Although the length of patient survival time from initial diagnosis is longer for those with secondary GB, once the stage of GB is reached the prognosis for both forms is equally dismal when adjusted for age [7,8]. TP53 mutations are rare in primary GB. Typical of primary GB are the amplification of the epidermal growth factor receptor (EGFR) gene and mutation or loss of the phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene [6-9,10]. Contrary to this, a high proportion of secondary GB exhibit TP53 and isocitrate dehydrogenase 1 (IDH1) mutations and alterations of EGFR and PTEN are infrequent [11-13]. More recently, high resolution genomic studies have identified four molecular GB subtypes (proneural, neural, mesenchymal and classical) that are associated with specific genetic and prognostic features [14].

Significant advances in neurosurgical techniques, radiotherapy and chemotherapy have provided brain tumor patients with prolongation of their lives, greater maintenance of cognitive and motor function, decreased disfigurement, low peri-operative mortality and post-operative rates of infection [15]. Unfortunately, the median survival time is poor for GB patients (12-15 months) [15-17]. There are multiple obstacles that prevent the complete eradication of GB by conventional therapies. GB diffusely infiltrate neighbouring brain tissue, often several centimeters from the primary tumor mass [18]. As a consequence, GB patients are rarely cured of their tumors by surgical intervention [19]. Radiotherapy and chemotherapy offer limited extension of survival and tumor burden reduction, likely as a result of the development of resistance to the therapies [20,21]. To circumvent these limitations, some researchers have focused their efforts on exploiting the power of the immune system to eradicate GB [22-24].

Conceptually, GB are ideally suited for immune therapeutic intervention. Although GB is locally invasive, they rarely disseminate outside the CNS [25]. The containment of GB within the cranial vault should increase the exposure and thus the susceptibility of GB cells to locally administered immune therapeutic agents and/or immune effector cells. In addition, multiple glioma-associated antigens (GAA) [26] have been identified that allow for the selective targeting of malignant cells by T cells that spare the normal brain cells required for maintaining cognitive and motor functions. The detection of immunosuppressive molecules and immune cell infiltrates in GB provide the rationale for inhibiting these sources of immune suppression or for the stimulation of potent anti-tumor immune responses [27].

Amongst the various forms of immunotherapy, adoptive T cell therapy (ATCT) is able to circumvent some of the immunosuppressive mechanisms exhibited by GB [27]. With ATCT, T cells are trained or genetically engineered *ex vivo* to react to tumor antigens then expanded prior to reinfusion to the patient [28]. The *ex vivo* manipulation of T cells ensures that they are properly stimulated and differentiated into armed effector cells prior to their adoptive transfer. In clinical trials, ATCT has yielded promising results when applied immediately after surgical tumor debulking, most likely because the adoptively transferred T cells home to and destroy infiltrating pockets of GB cells [29]. Here, an overview of various ATCT approaches developed and tested is provided.

Non-human leukocyte antigen (HLA) restricted T lymphocytes

The cloning of the T cell growth and differentiation gene IL-2 paved the way for *ex vivo* expansion of large quantities of lymphokine activated killer (LAK) cells [30]. LAK cells are generated by culturing lymphocytes in high concentrations of recombinant IL-2 for 3-7 days. Since leukapheresis, an expensive procedure, is required to obtain therapeutic numbers of LAK cells some GB patients may be restricted from receiving this therapy. Following *ex vivo* expansion, LAK cells are infused directly into to the brain cavities created by tumor resection or normal brain tissue surrounding the cavities as LAK cell migration to tumor sites is limited [31,32]. *In vitro*, LAK cells display non-HLA restricted lysis of glioma cells but not autologous peripheral blood lymphocytes [31-33]. Phase I trials revealed that the infusion of high numbers of LAK cells with IL-2 produced minimal toxicity to patients that included headache, fever and lethargy [31-34]. In one of the more promising trials, 5 recurrent GB and 4 anaplastic astrocytoma (AA) patients received repeated intracranial administrations of LAK cells and IL-2. Following immunotherapy the patients were offered chemotherapy. The median survival time was 53 weeks and 25.5 weeks for GB patients treated with chemotherapy alone [30]. These findings suggest that immunotherapy might eliminate chemotherapy resistant tumor cells as the immunotherapy plus chemotherapy group showed a 2 fold increase in survival. Results of a more recent LAK cell trial yielded a 1 y survival rate of 34% for recurrent GB patients [35]. This same research group treated GB patients that had no evidence of tumor progression following primary treatment. Impressively, the LAK cell therapy yielded a 75% 1 y survival rate. Detailed analysis of the data showed that patients benefited the most when they were infused with high numbers of CD3+/CD16+/CD56+ (T-LAK) cells and when patients did not take corticosteroids in the month prior to leukapheresis as corticosteroids inhibit LAK cell activity [36]. With these promising results, a randomized double arm Phase II clinical trial evaluating single dose intracavitary autologous LAK cells to Gliadel® wafer implants in newly diagnosed GB patients (NCT00814593) was conducted and the findings of this study are pending.

Tumor infiltrating lymphocytes

Dr. Rosenberg and colleagues pioneered the *ex vivo* expansion of autologous tumor infiltrating lymphocytes (TIL) with IL-2 for the adoptive cellular therapy of malignant melanomas [37]. TIL are thought to represent a population of *in vivo* activated and tumor-specific effector cells. Since TIL do not suppress tumor growth, it is postulated that tumors actively suppress TIL proliferation and lytic activity. *Ex vivo* TIL expansion with IL-2 enhances the number of cytotoxic lymphocytes available for adoptive cell transfer. Although IL-2 facilitates the large-scale expansion of TIL, this process requires 14-100 days [38] and cytolytic activity declines with time [39]. A therapeutically attractive advantage of TIL relative to LAK cells is their homing capacity to distal tumor sites [32]. The first use of TIL for recurrent high grade gliomas yielded promising patient responses [40]. The TIL was infused through an Ommaya reservoir at the time of tumor resection. Adoptive TIL transfers were supplemented with intracranial IL-2 infusions three times a week for one month. Patients exhibited transient low grade fever and asymptomatic hydrocephalus. Three of six patients experienced complete or partial responses with survival times exceeding 45 months. Although this approach has largely been abandoned, TIL may prove useful when used in conjunction with immune checkpoint inhibitors that prevent tumors from suppressing T cell functions [41].

Allogeneic T lymphocytes

Extensive efforts are taken to prevent the potent immunologic responses that threaten life and lead to the rejection of whole organs in transplant recipients. A clever approach was designed to exploit alloreactive T cell responses to treat high grade malignant gliomas [42]. With this approach, peripheral blood mononuclear cells (PBMNC) from healthy donors are mixed with lethally irradiated glioma patient PBMNC. The mixed lymphocyte reactions allow for the expansion of alloreactive cytotoxic T lymphocytes (aCTL) that recognize patient HLA antigens in bioreactors [43]. Tumor specificity is achieved since normal brain cells express little or no HLA class I while brain tumor cells do [44]. Another advantage is that abundant numbers of aCTL are readily obtained within two weeks as the CTL precursor frequency is often several logs higher if the immune responses engendered are to mismatched HLA antigens rather than self HLA: peptide complexes [45]. One immune escape route that could minimize the efficacy of aCTL therapy is the loss of HLA class I expression [27].

In vitro and *in vivo* studies demonstrated that aCTL displayed potent lytic activity towards human and rat GB cells and extended survival or cured GB-bearing rats [42-44,46-48]. Based on these studies, a Phase I clinical trial was performed involving local adoptive immunotherapy with recombinant human IL-2 and aCTL [44]. Six recurrent glioma patients (3 GB and 3 AA) received multiple administrations of intracavitary aCTL over a 10-month period following surgical debulking. Transient toxicities were recorded according to the NCI common toxicity scale criteria. One patient survived 40 months from the start of immunotherapy. At present, two others are alive without evidence of tumor recurrence at more than 15 years from the start of immunotherapy [49]. A dose escalation trial involving intratumoral adoptive transfer of aCTL is ongoing for recurrent high grade glioma patients (NCT01144247). Following surgery, aCTL will be placed in the resection cavity. Later patients will be treated with 2 aCTL infusions, 7 days apart to complete 1 cycle. Patients may receive up to 5 treatment cycles that are given every other month. The aCTL will be derived from different healthy donors at each cycle who are allogeneic to the patients.

Autologous tumor antigen sensitized T lymphocytes

A limited number of studies explored the use of autologous tumor-sensitized lymphocytes [50-52] for recurrent high grade gliomas. In this approach glioma patient PBMNC were activated and expanded by co-culturing lethally irradiated glioma cells with PBMNC in the presence of IL-2. The lymphocytes were infused via an Ommaya reservoir into the resected tumor beds. Rapid tumor regressions ensued with temporary fever in some patients and minor local hemorrhage in one patient [50-52]. Although promising, this approach is restricted by the need for autologous tumor tissue which is not possible for those patients with inoperable tumors. In addition, tumor heterogeneity in terms of GAA expression may limit the efficacy of this approach as not all tumor cells within a tumor mass are able to survive in culture to stimulate T cell responses directed to all the GAA expressed by the tumor in situ.

A more recent and interesting clinical study evaluated the adoptive transfer of autologous cytomegalovirus (CMV)-specific T cells to

recurrent GB patients [53]. The rationale for this approach is based upon the controversial observation of CMV antigen expression in GB cells but not surrounding normal brain cells [54]. In proof-of-concept experiments, the *ex vivo* expansion and specificity of CMV-specific T cells from seropositive GB patients was demonstrated [55- 57]. The treatment of one recurrent GB patient with CMV-specific T cells and temozolomide was coincidental with long-term disease free survival and thus justifies formal testing of this approach [56]. In Phase I testing, CMV-specific T cells were generated in the presence of IL-2 by co-culturing freshly isolated patient PBMNC with autologous PBMNC pre-sensitized to synthetic CMV peptides at a 2:1 responder to stimulator ratio [53]. Most patients received 3-4 T cell infusions. Of the 19 patients enrolled, CMV-specific T cells were successfully expanded from 13 patients. The time to progression for all patients after infusion was variable with a median of 246 days and an overall median survival of 403 days. Interestingly, one patient showed nearly a 4 y progression free survival time after the last T cell infusion and remains disease-free [53]. Importantly, the therapy was well tolerated with mild to moderate headache, fatigue, lymphopenia, seizure and one severe case of transient seizure that was found to be unrelated to the therapy. CMV-specific T cells isolated from tumor infiltrating T cells from one patient that progressed on therapy showed that the antigen-specific cells had weak cytolytic activity and they expressed T cell exhaustion markers. This observation suggests that CMV- specific T cells are actively suppressed and that immune checkpoint inhibitors might prevent tumors from evading CMV-specific T cells [41]. Further testing of this approach is warranted.

Chimeric antigen receptor T cells

Melanoma and glioma cells express common differentiation antigens that are presented on class I HLA molecules [58] and thus provide the rationale for vaccination strategies that induce T cell responses to these differentiation-associated antigens. One limitation of targeting GAAs is that tumors evade T cell recognition by down regulating their expression of the GAAs and/or HLA class I alleles [27]. An attractive and alternative approach is to genetically engineer T cells to recognize GAA in an HLA-independent manner.

Chimeric antigen receptor (CAR) T cells are tumor-specific T cells that bear a unique receptor composed of a fusion between a B cell receptor and intracellular signaling domains that promote T cell proliferation and activation [59]. The general design of CARs includes a single chain variable fragment (scFv), a hinge region and intracellular costimulatory signaling domains. The scFvs are derived from antibodies with high specificity and affinity towards an antigen of interest and are a combination of antibody heavy- and light-variable regions joined by a hinge region. The intracellular costimulatory signaling domains derived from CD28 and CD3 are in place to provide signals that induce T cell activation, proliferation and cytokine secretion [59]. Fourth generation CARs (TRUCKs) are designed to express costimulatory ligands and cytokines that ultimately enhance T cell proliferation and cytolytic activity [60]. To generate CAR T cells, autologous T cells are stimulated and activated *ex vivo* with IL-2 and CD3 and CD28 antibodies [60]. The T cells are then transduced with virus containing a specified CAR gene vector and the resulting T cell clones are expanded with IL-2 and infused in to the patient [60].

Multiple GB cell surface antigens have been identified as potential targets for CAR T cell therapies [59]. CAR T cells have been developed for antigens expressed by a high percentage of GB that include EGFRvIII [61,62], IL13Ra2 [63,64], EphA2 [65] and HER-2 [66]. Preclinical studies have shown that CAR T cells target antigen bearing GB cells and they suppress tumor growth in preclinical animal models [63-65,67,68]. The first pilot CAR T cell study in humans was recently completed [69]. In this study, IL13Ra2 CAR T cells were generated as IL13Ra2 is overexpressed in more than 50% of GB while weak expression was noted on normal brain cells [70]. The ability to safely target IL13Ra2 in GB served as the basis for the design and generation of IL13Ra2-specific CAR T cells, termed IL13-zetakine [71]. The IL13-zetakine T cells generated showed specificity to targets expressing IL13Ra2 and an activated effector T cell phenotype as the cells were positive for CD3, CD8, CD45RO, CD69, and CD95 and the cells were negative for T cell exhaustion markers (PD-1 and KLRG-1) [69]. Repeated intracavitary infusions (12 infusions) of IL13-zetakine T cells with a maximum tolerated dose of 10^8 T cells per infusion induced transient brain inflammation. Interestingly, the degree of brain inflammation appeared to correlate with the degree of IL13Ra2 expression in the tumors. Promising anti-tumor responses were observed in the small group (n=3) of patients treated in this dose-escalation trial. Generation of clinically relevant numbers of IL13-zetakine T cells is cumbersome and takes approximately 3-4 months thus limiting the utility of CAR T cells for recurrent GB patients. As recurrent GB patient survival time is short, investigators are considering the use of pre-engineered "off-the-shelf" allogeneic CAR T cells to circumvent this limitation [69]. Insight gleaned from this pilot study will provide the basis for further refinements of IL13-zetakine T cell therapy [69]. Based upon detailed preclinical studies, a phase I study with CAR T cells directed to EGFRvIII in patients with residual or recurrent GB was recently announced [67]. The clinical use of biCAR T cells recognizing two tumor antigens may further improve the efficacy of CAR T cell therapy as antigen loss as an immune evasion mechanism is lessened with biCAR T cells [68].

Conclusion

The ability of multiple types of effector T cells to suppress GB growth in preclinical and clinical studies provides the impetus for further testing and refinement of T cell therapies. GB patients will likely continue to benefit most from ATCT when applied immediately after tumor resection as tumor burden is low. Some ATCT clinical studies support ATCT in newly diagnosed GB patients or in combination with chemotherapy. The incorporation of checkpoint inhibitors might revive the clinical use of TIL and tumor-sensitized T cell therapies. CAR T cell technology has shown promise in targeting the most common GB-specific antigens. Importantly, to avoid antigen-loss as an immune evasion strategy, CAR T cells can be directed towards multiple tumor antigens. Fine-tuning of the current T cell therapies offers great hope for GB patients.

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