ONCOIMMUNOLOGY
2016, VOL. 5, NO. 6, e1145332 (19 pages)
http://dx.doi.org/10.1080/2162402X.2016.1145332

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REVIEW

Prioritization schema for immunotherapy clinical trials in glioblastoma

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ABSTRACT

Background: Emerging immunotherapeutic strategies for the treatment of glioblastoma (GBM) such as dendritic cell (DC) vaccines, heat shock proteins, peptide vaccines, and adoptive T-cell therapeutics, to name a few, have transitioned from the bench to clinical trials. With upcoming strategies and developing therapeutics, it is challenging to critically evaluate the practical, clinical potential of individual approaches and to advise patients on the most promising clinical trials.

Methods: The authors propose a system to prioritize such therapies in an organized and data-driven fashion. This schema is based on four categories of factors: antigenic target robustness, immune-activation and -effector responses, preclinical vetting, and early evidence of clinical response. Each of these categories is subdivided to focus on the most salient elements for developing a successful immunotherapeutic approach for GBM, and a numerical score is generated.

Results: The Score Card reveals therapeutics that have the most robust data to support their use, provides a reference prioritization score, and can be applied in a reiterative fashion with emerging data.

Conclusions: The authors hope that this schema will give physicians an evidence-based and rational framework to make the best referral decisions to better guide and serve this patient population.

ARTICLE HISTORY
Received 16 November 2015
Revised 12 January 2016
Accepted 16 January 2016

KEYWORDS
Clinical trial; glioblastoma; immunotherapy; prioritization; score card

Introduction

The current standard of care for GBM is maximal safe resection followed by adjuvant chemoradiation therapy. Despite recent advances in treatment and aggressive therapy, the median survival time remains slightly over 14 mo.[1] Although these therapies prolong progression-free survival, recurrence is inevitable. Moreover, the nonspecific nature of conventional therapy for GBM often results in incapacitating damage to surrounding normal brain tissue. Despite scientific breakthroughs in our understanding of this disease, only modest improvements in survival have been achieved over the past 30 y. Interestingly, several immunotherapeutic strategies have transitioned from the bench to clinical trials. Although this is an exciting time in brain tumor immunotherapy, practitioners face a unique and difficult challenge in advising GBM patients on the most promising clinical trials. Frequently, the practitioner must guide this decision without sufficient information or understanding of how well a particular approach has been vetted. In addition, while there have been numerous early phase studies in the field, there is also a recognized wastage of valuable resources and time, as patients enroll onto trials out of desperation that may not have been sufficiently considered. Specifically in GBM there have been hundreds of studies that could have been aborted early on. The pace of development of immunotherapies in oncology, including GBM, is faster than the traditional pace of drug development, given the recognized need and patient and advocacy enthusiasm. It is difficult therefore to prioritize preclinical approaches that are rapidly progressing to clinical trial implementation, as potentially ineffective approaches could be rushed into development. Therefore, we propose a system to prioritize such therapies in an organized and data-driven fashion.

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Supplemental data for this article can be accessed on the publisher's website
Unpublished papers cited:
1. Personal communication from Dr Elizabeth Grimm.

This schema is based on four categories of factors: robustness of the antigen target, ability to activate and sustain immune responses in the glioma microenvironment, preclinical vetting, and early evidence of clinical response (Table 1). Each category is subdivided to focus on the most salient elements for developing a successful immunotherapeutic approach for GBM, and a numerical score is generated. Considering the significant heterogeneity of GBMs, this system will ultimately favor combination strategies, as they are more likely to result in a meaningful outcome. This score card, which includes current immunotherapy trials for GBM patients, reveals which therapeutics have the most robust data to support their use, provides a reference prioritization score, and can be applied in a reiterative fashion with emerging data. The rationale of the score card's use can potentially be applied in a forthcoming global adaptive Bayesian clinical trial in GBM.[2] The use of the score card also intends to encourage preclinical vetting and rationally selected combinatorial approaches for translational researchers and industry.

Methods

Therapeutic selection

Current immunotherapy trials in GBM were identified through a systematic search on www.clinicaltrials.gov using the following keywords: "GBM" AND "immunotherapy" or "glioma" AND "immunotherapy." The two initial searches yielded a combined total of 121 studies, many of which were duplicates. Nine trials were eliminated that did not have a primary immune therapeutic intent (e.g., PET imaging in patients treated with chemoradiation or immunotherapy, MR imaging in patients treating with DC therapy, evaluation of factors in human brain tumors) or were targeted to other cancers such as cholangiocarcinoma, grade II glioma, diffuse intrinsic pontine glioma, ependymoma, and medulloblastoma/neuroectodermal tumors (i.e., they were misclassified). Two trials were listed in duplicate (TVI-Brain-1), both as a phase I and a phase II clinical trial (NCT01290692/NCT01081223). Six trials were eliminated that involved oncolytic viruses, which did not have an immunotherapeutic intent (AdV-tK/radiation, DNX-2401, HSV G207). Three studies had been terminated (IMA-950, IMA-950 and poly-ICLC, tumor-specific hybridomas). A phase I clinical trial of the IDH1 peptide vaccine (NCT02454634) was included in the Appendix, given that there is an active recruitment of grade IV gliomas in addition to grade III gliomas in this trial. Several trials evaluating the immune checkpoint inhibitors in GBM were not listed on either of the searches, and had to be searched for separately on www.clinicaltrials.gov using search terms "pembrolizumab" AND "GBM," "nivolumab" AND "GBM," "ipilimumab" AND "GBM." Six trials (NCT02209376, NCT02026271, NCT02331693, NCT01904123, NCT02365662, NCT0181192) were also not listed in either of the searches on www.clinicaltrials.gov and had to be searched for separately using search terms "EGFRvIII" AND "chimeric antigen receptor," "IL-12 adenovirus" AND "GBM," "EGFR CAR" AND "GBM," "STAT3" AND "GBM," "ABBV" AND "GBM," "Adv-TK" AND "Adv-Flt3L" AND "GBM." Therefore, after eliminating duplicates, the complete search yielded a combined total of 68 trials, 34 of which were open and 34 of which were closed (Appendix 1).

In order to obtain more information on each of the immunotherapeutics in the aforementioned trials, each agent was then searched for via PubMed (with defined key search "name of agent" AND "glioma," "name of agent" AND "GBM," "name of agent" AND "cancer," "name of agent" AND "brain"), the source data assessed for results related to the Score Card, and documented in the references listed in Tables 2 and 3. For the vetting of preclinical approaches, a search was then performed using the terms "GBM" AND "immunotherapy," only eliminating review articles. Once these preclinical agents were found, a more specific PubMed search was undertaken regarding each preclinical agent of interest (with defined key search "name of agent" AND "glioma," "name of agent" AND "GBM," "name of agent" AND "cancer," "name of agent" AND "brain"). The source data were assessed for results related to the Score Card and documented in the references listed in Tables 2 and 3. Our literature review adapted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[3] to minimize potential bias in the identification, selection, synthesis and summary of studies, and enhance the quality and transparency of our review.

Table 1. Prioritization "Score Card" for glioblastoma immunotherapeutics.

Target	Frequency of target expression	0–33% (1) 34–66% (2) 66–100% (3)
	Therapeutic targeting has benefit in other malignancy	1
	Homogeneous tumor expression	1
	Expression is sustained at recurrence	2
	Mechanism of resistance	1
	Specificity of expression in the tumor	1
Immune activation and effector response	Activating component (i.e., costimulation, TLR)	1
	Trafficking to the tumor microenvironment	1
	Maintenance of effector response within tumor	1
Agent: Preclinical	Glioma cancer stem cell activity	2
	Efficacy in preclinical model	Other model (1) Clonotypic (1) Xenograft/*GEMM (2)
	Acceptable toxicity profile	2
	Hits target (if known) *in vivo*	2
Agent: Clinical	Clinical activity in GBM	3
	Extreme responders	2
	Combinatorial data	2
	Acceptable phase I safety data	2

Abbreviation: *GEMM, genetically engineered murine model (of glioma).

Explanation and justification of score card

The components of the score card are based on characteristics that the authors believe are necessary to generate an optimal, antitumor immune-therapeutic response (Table 1). In order to ensure that the scoring system is properly balanced, three experts in the field evaluated the categories and provided point assignments for each category to be used in the score card, which was then reviewed by a biostatistician (SZ). First, an

Table 2. Priority scores for glioblastoma immunotherapeutics with published clinical data.

							Immune checkpoints				Adoptive cellular				
	Therapeutic approach		CDX 110	TGF-β Anti-sense	HSP-96	EGFR Ab	Anti-CTLA-4	Anti-PD-1PD-L1	Anti-IL-2Rα	CSF-1R inhibitor	DCs	NK/LAK	CMV T cell	IL13Rα 2CAR	IL-12
Antigen/ Target	Expression frequency	0–33% (1) 34–66% (2) 66–100 (3)	1[23-25]	3[126]	3[105,127]	2[26,128,129]		1[10]		1[130]	3[15-17,131]		3[15-17,131]	3[132,133]	
	Benefit in other malignancy	1		1[134-136]	0[14,137]		1[47,138]	1[48,139-144]		1[59,60]	1[145-147]			1[148-150]	1[94]
	Homogeneous expression	1			1[105,127]	1[26,128,129]				1[57,151]	1[16,17,131]			1[132,133]	
	Persistence at recurrence	2	2[152,153]	2[126]		2[26,128,129]		1[9]			2[65]	2[65]			
	Mechanism of resistance	1	1[152,153]			1[26,128,129]									
	Specificity of expression in the tumor	1	1[23-25]								1[23-25]			1[132,133]	
Immune activation and effector response	Immune activation	1	1[4,5]		1[127]	1[154]	1[155-157]				1[22,31,34,35,37,38,40]		1[65]	1[158]	1[89-91]
	Trafficking to the tumor	1	1[159]		1[105]		1[155-157]	1[8]		1[58,160,161]	1[22,34,35,37,40]		1[65]	1[158]	1[89,91]
	Maintenance of effector response within tumor	1			1[105]		1[8,157]	1[8,162]			1[22,34,35,37,40]			1[158]	1[89]
Agent:Preclinical	Anti-stem cell activity	2		2[163,164]		2[165]					2[166-168]			2[169]	2[92]
	Efficacy in preclinical models	Other (1) Clone (1) Xenograft/* GEMM (2)	1[170,171]2[4]	1[43-45]2[164]		1[165]2[154]	2[8,155,172,173]	2[8,162]	1[53]2[174]	1[58,160]1[58,160]2[58,160]	1[22]1[22,34,35,37,40]2[22]	1[175-177] 2[178,179]	1[61,65]	1[169]2[158]	1[89,90] 2[89,90,180]
	Acceptable toxicity profile	2	2[4,159,181]	2[182]	2[105]	2[154,183]	2[47,184-190]	2[48,49,139-144]	2[54,174]	2[58,60,160]	2[22,40,98,191-195]	2[62,63]	2[65]	2[70]	2[90,93,196]
	Hits target *in vivo*	2	2[4,197]				2[8,172,173]	2[8,162]	2[174]	2[58,160]	2[22,37]	2[178,179]		2[158,169]	2[90]
Agent: Clinical	Clinical activity in GBM	3	3[27,29]	3[46]	3[104,105]				3[54]		3[22,30-35,98]	3[62-64]	3[60,64]	3[70]	
	Extreme responders	2	2[29]	2[45]	2[104]		2[198]	2[48]			2[22,30,31]		2[60,64]		
	Combinatorial data	2	2[28,29]		2[104]	0[183,199]	2[51]		2[54]		2[22,30-33]		2[61]		
	Acceptable phase I safety data	2	2[159,181]	2[46,200]	2[105]	2[183,199]	2[47,138,184-190]	2[48,49,139-144]	2[54]	2[60]	2[22,30-33]	2[62-64]	2[65]	2[70]	2[94]
Score			23	20	18	16	16	15	14	14	30	12	19	23	15

Abbreviation: *GEMM, genetically-engineered murine model (of glioma).

Table 3. Priority scores of glioblastoma immunotherapeutics in preclinical studies.

Therapeutic agent					Adoptive cellular							
			STAT3 inhibitor	EGFRvIII × CD3 bispecific monoclonal Ab	*EGFRvIII CAR	*EGFRCAR	*IDH1 peptide vaccine	4-1BB aptamer	*Arginine	*IDO inhibitor	Adv-TK + Adv-Flt3L
Antigen/ Target	Expression frequency	0–33% (1) 34–66% (2) 66–100 (3)	2[72]	1[23-25]	1[23-25]	2[26,128,129]	1[85,86]			3[201,202]	
	Benefit in other malignancy	1	1[203-211]								
	Homogeneous expression	1				1[26,128,129]					
	Persistence at recurrence	2	2[212]	2[152,153]	2[152,153]	2[26,128,129]	2[85,86]				
	Mechanism of resistance	1	1[212]	1[152,153]	1[152,153]	1[26,128,129]				1[202]	
	Specificity of expression in the tumor			1[23-25]	1[23-25]		1[85,86,213]				
Immune activation and effector response	Immune activation	1	1[111,214]	1[84,215]	1[69,216]	1[217]	1[87,218]	1[172,219-221]	1[109,110]		1[95,96]
	Trafficking to the tumor	1	1[214,222]	1[84,215]	1[66-68,216]	1[223]	1[87,218]	1[224]			1[95,96]
	Maintenance of effector response within tumor	1	0[214]	1[84,215]	1[66,67,216]		1[87]	1[172]	1[110]		1[95,96]
Agent: Preclinical	Anti-stem cell activity	2	2[7,79-81]			2[223]					
	Efficacy in preclinical models	Other (1) Clone (1)* GEMM/Xenograft (2)	1[111,214] 1[7,76,80,111,210,214] 2[112,225]	2[84,215]	1[66-69]2[66-69,216]	1[217]2[223]	1[218]2[87,218]	1[219,224,226]2[172,224]		1[202]2[8,202]	1[95]2[96]
	Acceptable toxicity profile	2	2[78,112,225]	2[84,215]	2[66-68,216]	2[217,223]	2[87,218]	2[172,224,227]	2[228]	2[8]	2[95,96]
	Hits target *in vivo*	2	2[112,210,225]	2[84,215]	2[66-68,216]	2[223]	2[87,218]			2[8]	2[95,96]
Score			20	14	15	17	14	8	4	11	10

Abbreviation: *GEMM, genetically-engineered murine model (of glioma).

appropriate target is required, and the ideal target would be specific to the tumor and have a high frequency of expression. Additionally, target/antigen expression would preferably be homogeneous (with ubiquitous or near ubiquitous staining on immunohistochemistry) versus occurring as isolated islands of the antigen deposited in the tumor mass, to prevent negative clonotypic selection.[4,5] Other desirable immune targets would be those that remain present at the time of tumor recurrence after standard-of-care therapy.

Generation and maintenance of a robust immune response are also critical components of a successful immunotherapeutic. Treatments/agents should be able to activate the immune response (e.g., T-cell signal, proinflammatory cytokines, toll-like receptor (TLR) agonists, DCs), support infiltration of the tumor site, and sustain immune effector function within the tumor microenvironment. Studies that have shown a lasting immune response in the setting of a tumor rechallenge *in vivo* or an antitumor immune response that results in a durable survival advantage were included in the score card. If there are no published data showing that the agent generates or maintains an immune response, then the categories are left blank. If the agent failed to generate or maintain an immune response, the category is scored as 0. It is clear that all of these attributes may be difficult for a single agent to achieve given that GBMs are notoriously heterogeneous regarding antigen expression, effector responses, and immunosuppressive mechanisms; hence, this scoring system favors combinatorial treatment strategies, which are more likely to impact a greater number of patients and result in longer, durable responses.

Prior to advancing to clinical trials, the approach/agent should be vetted in preclinical testing—ideally in a variety of models. In the score card, credit was given to agents tested in multiple animal model systems. The xenograft and genetically engineered murine models (GEMMs) were weighted with more points since they potentially are more representative of human biology and recapitulate tumor heterogeneity. Furthermore, the agent ideally should demonstrate effector function in the glioma microenvironment. The role of glioma stem cells (GSCs) in tumor immunosuppression has been established (i.e., inhibition of T-cell activation, induction of regulatory T cells, and initiation of T-cell apoptosis[6,7]); therefore, a treatment strategy inhibiting GSCs will likely have a therapeutic advantage, and thus this was included in the assessment. Finally, safety is paramount, but given the dire prognosis of GBM, certain toxicities may be more acceptable, although it is challenging to define a threshold level. For immunotherapeutics that have advanced to phase II clinical trials, we took several additional factors into consideration. A clearly favorable clinical outcome in GBM patients and an acceptable safety/toxicity profile in phase I studies were weighed heavily. Additionally, clinical trial results that demonstrated the presence of extreme responders (i.e., patients with significantly lengthened survival times) were given special consideration and were a component of our analysis. As mentioned above, because successful initiation and maintenance of an adequate antitumor immune response are difficult for a single immunotherapeutic agent to achieve, combining immunotherapeutic strategies presents a feasible way to enhance the antitumor response (e.g., blockade against indoleamine 2,3-dioxygenase [IDO], programmed cell death ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated antigen 4 [CTLA-4],[8] or intratumoral IL-12 combined with CTLA-4 blockade). Additionally, any new immunotherapeutic will be better received if it can be easily and safely combined with conventional treatment regimens. With this in mind, agents for which there were combination therapy data were given additional points because these, in the authors' opinion, are most likely to have a meaningful therapeutic response.

Arbitration of conflicting data

In several instances, the use of the score card was confounded by conflicting reports. For example, in determining the target frequency score of PD-L1, one study found nearly ubiquitous staining,[9] thus resulting in a score of 3; however, another study found significantly less[10] staining, rendering a score of 1. Because there were concerns regarding the antibody staining in the former study, the results were ultimately scored based on the second study, which was also more aligned with the findings of PD-L1 expression in other solid malignancies.[11,12] Another example occurs in the setting of therapeutic benefit found in phase II clinical trials of heat shock proteins in patients with solid malignancies, but ultimately phase III studies failed to confirm these results in melanoma and renal cell carcinoma.[13,14] As such, the phase III data were prioritized and the benefit in other malignancies was scored as 0. Yet there is an active phase II clinical trial evaluating heat shock protein in GBM (NCT02122822).

Additionally, the association between cytomegalovirus (CMV) and GBM has remained controversial.[15-17] There is not a uniform consensus in the scientific community regarding the expression of CMV in GBM.[18-20] Regardless of the conflicting data, two clinical trials focused on targeting CMV in GBM have emerged, including the use of valganciclovir hydrochloride[21] and DC immunotherapy against CMV antigen pp65.[22] For the purposes of this paper, adoptive cellular approaches that target CMV received the highest score (3) on antigen expression given the recent data (Table 2).

Clinical versus preclinical designation

If the approach had entered clinical trials in other malignancies and/or is in phase I or II trials for GBM patients, with published results, then the assignment was made to the clinical score card (i.e., IL-12). If the approach was not tested in other malignancies and/or is in phase I testing, without reported data, then the approach was classified as preclinical (i.e., IDH1 peptide).

Results

Overall, phase III immune therapeutic strategies scored the highest

The DC-based strategies and the EGFRvIII peptide vaccine (CDX 110) had the highest priority scores (Table 2), and both are in final phase III clinical trial testing. These agents have been vetted preclinically and have been efficacious in phase II clinical trials. CDX 110 peptide vaccine targets the tumor-

specific antigen epidermal growth factor receptor variant III (EGFRvIII).[4] The mutant is ligand independent and constitutively active, resulting in sustained activation of oncogenic pathways, but is only found in approximately a 30% of GBMs.[23-26] Restriction of EGFRvIII to GBM has made it an excellent target for immunotherapy, but treatment failure corresponds to the loss of the antigenic target, and only a select subset of patients could benefit[27] (i.e., EGFRvIII-positive patients). CDX 110 has been extensively studied in phase II clinical trials, with prolonged survival in patients with newly diagnosed GBM compared to historical controls[27-29] and has completed phase III testing, with the final results pending.

In contrast, DC vaccinations typically include multiple antigenic targets and do not require biomarker selection. The basic strategy for DC vaccination is to give the patient autologous DCs that have been manipulated *ex vivo* to present autologous tumor antigens. DC administration has varied by route, schedule, and combination with other treatment modalities. Vaccination with DCs is safe and has been well tolerated in patients.[22,30-33] Some studies have shown clinical responses, either in tumor regression or improved survival relative to historical or contemporary controls.[22,31,34-36] Immune responses have also been demonstrated with the use of surrogate endpoints.[22,31,34-39] In patients who underwent reoperation after vaccination with DCs, some had infiltration of cytotoxic T cells within the tumor.[35,40] Although there are no published data yet on the DCVax phase II trial, it has moved to phase III clinical testing. The most recent *Nature* paper by Mitchell *et al.*[22] showed that preconditioning the vaccine site with tetanus/diphtheria (Td) toxoid, a potent recall antigen, can significantly improve the lymph node homing and efficacy of tumor-antigen-specific DCs, and these patients (n = 6) had median survival times that exceeded 40 mo. This report enhanced the score of this approach.

Yet, use of trabedersen or AP 12009 (a TGF-β antisense compound) did not score as highly compared to the other phase III immunotherapeutic strategies, despite an ongoing phase III SAPHIRRE study. The transforming growth factor 2 (TGF-β2) is overexpressed in more than 90% of malignant gliomas, and its levels are closely related to tumor progression.[41,42] Inhibition of TGF-β2 in tumor tissue leads to reversal of tumor-induced immune suppression as well as inhibition of tumor growth, invasion, and metastasis.[43,44] Trabedersen (AP 12009) has been studied in three phase I/II studies,[45] and a randomized, active-controlled dose-finding phase IIb study,[46] with established safety and efficacy. Trabedersen treatment of patients with recurrent high-grade glioma led to some long-lasting tumor responses, but trabedersen treatment does not activate or maintain an immune effector response, which contributes to its lower score relative to the other phase III immunotherapeutic strategies.

Immune checkpoints (CTLA-4, PD-1) rank equivalently

The immune system regulates itself using immune checkpoints, and these mechanisms are either upregulated or appropriated in GBM. When T cells are activated, they upregulate membrane CTLA-4 and PD-1 proteins. CTLA-4 competes with CD28 to bind B7, and PD-1 will bind to its ligand, PD-L1; both signals will inhibit ongoing T-cell activation. Blockage of these immune inhibitory pathways has emerged as a powerful immunotherapeutic strategy, and antibody-based targeting of immune checkpoints (checkpoint inhibitors) has been heavily investigated as single agents, or in combination. Commonly targeted checkpoints include: PD-1, CTLA-4, and regulatory T cells (Tregs). The use of blocking humanized monoclonal antibodies, such as ipilimumab (anti-CTLA-4), is FDA approved for treating patients with metastatic melanoma.[47] Antibody targeting of the PD-1/PD-L1 axis has also demonstrated robust preclinical efficacy in an established murine model of glioma, including in synergy with ipilimumab.[8] Anti-PD-1 antibodies (nivolimumab, pembrolizumab) have also been clinically tested in melanoma patients,[48-50] and have been FDA-approved for treating advanced melanoma and non-small cell lung carcinoma. The application of the score card did not reveal an advantage of one approach over the other (Table 2), but target elucidation indicates that only a subset of patients is likely to benefit in the context of monotherapy. It should be noted that although ipilimumab (anti-CTLA-4 antibody) has demonstrated prolonged overall survival in randomized phase III trials,[47] anti-PD-1 agents (pembrolizumab, nivolumab) have a better toxicity profile.[51]

The score of daclizumab, an antibody against IL-2Rα that depletes Tregs, ranked equivalently with the immune checkpoint inhibitors. Tregs are populations of T cells responsible for modulating immunity in a number of cancers, including GBM.[52] Daclizumab treatment was well tolerated in three patients, with no symptoms of autoimmune toxicity, and it resulted in a significant reduction in the frequency of circulating CD4+CD25+Foxp3+ Tregs in comparison with saline controls.[53,54] A significant inverse correlation between the frequency of Tregs and the level of EGFRvIII-specific humoral responses suggests that the depletion of Tregs may be linked to increased vaccine-stimulated humoral immunity.[54] Of note, daclizumab works by binding CD25, the α subunit of the IL-2 receptor, and therefore can target other CD25+ T cells as well as Tregs. Daclizumab has also been shown in multiple sclerosis to reduce CNS inflammation in randomized phase III clinical trials, possibly by targeting regulatory NK cells,[55] suggesting that this antibody has activity beyond just targeting Tregs.

The effectiveness of other immune modulatory agents, such as those targeting colony-stimulating factor (CSF-1), also ranked equivalently with the immune checkpoint inhibitors. Tumor-associated macrophages are associated with high tumor grade and poor prognosis in gliomas.[56,57] Macrophages depend upon CSF-1 for differentiation and survival; therefore, CSF-1R inhibitors represent an alternative strategy to target tumor-associated macrophages and microglia. In a mouse proneural GBM model, the use of a CSF-1R inhibitor dramatically increased survival, shrank established tumors, and slowed intracranial growth of patient-derived glioma xenograft.[58] PLX3397 and JNJ-40346527, both small molecule CSF-1R inhibitors, are currently being studied in other malignancies in clinical trials.[59] One published phase I/II study showed that CSF-1R inhibition was well tolerated, although preliminary antitumor results suggested limited activity as a monotherapy in the treatment of relapsed or refractory Hodgkin lymphoma.[60] Discussions are ongoing about the initiation of this strategy in GBM patients.

Adoptive cell-based strategies rank heterogeneously

Adoptive cell-based strategies, including DC therapy, CMV T-cell therapy, NK/LAK cells, EGFRvIII-CAR, IL13Rα2-CAR, and EGFR-CAR show heterogeneous ranking as a group, with a wide range of priority scores. Adoptive transfer therapy is a form of passive immunotherapy in which immune cells are activated and amplified *ex vivo* and administrated to a patient, either by systemic injection or directly into the tumor or tumor resection cavity. Cytotoxic T lymphocytes (CTLs), lymphocyte-activated killer cells (LAK), and genetically-engineered T cells expressing chimeric antigen receptors (CARs) have all been used for this. The first is based on the trafficking of tumor antigen-specific T cells to the desired malignant target. To accomplish this, autologous tumor-specific CTLs are collected, activated *ex vivo*, expanded, and then readministered to the subject. LAK cells are natural killer (NK) cells and NK T-like cells that, when stimulated with IL-2, become nonspecific tumoricidal cells. Several phase I and II studies have exploited this tactic in the treatment of GBM.[61-65] For example, autologous CMV-specific T-cell therapy is safe, with minimal side effects, and may offer clinical benefit for patients with recurrent GBM. During one study,[65] 4 of 10 patients who completed the treatment remained progression free.

Genetically engineering T cells to express CARs, fusion proteins that combine the single chain variable fragment of naturally occurring monoclonal antibodies with the signaling molecules that act downstream of TCR engagement, redirect T-cell specificity to surface tumor-associated antigen independently of MHC presentation. Two CAR T-cell therapies, targeting EGFRvIII and IL13Rα2, have been shown to be efficacious in murine model systems of glioma and CNS melanoma.[66-69] As such, the EGFRvIII-CAR (NCT02209376, NCT01454596) and IL13Rα2-CAR (NCT02208362) are being investigated in phase I clinical trials in GBM. Moreover, a pilot study of three patients treated with intracranial delivery of IL13Rα2-specific CAR T cells for recurrent GBM demonstrated safety and feasibility with transient antitumor activity for some patients.[70] Currently, CAR T cell therapies are limited to antigens restricted from normal tissue expression, to avoid on-target, off-tissue toxicity. However, preclinical studies have shown CARs can be generated to fine tune T-cell activity to the level of EGFR expression in which a CAR with reduced affinity can enable T cells to distinguish tumor from non-tumor cells, potentially expanding application of CAR T cells to additional targets.[71] Of the CAR approaches thus far devised, the IL13Rα2 faired best, ranking similarly to CDX 110, based on more advanced clinical development, the ubiquity of the target, and the anti-stem-cell properties. The EGFR CAR and EGFRvIII CAR strategies however ranked similarly among the preclinical therapeutic strategies.

STAT3 inhibition ranks high among preclinical therapeutic strategies

The STAT3 pathway is a potent regulator of tumorigenesis, tumor-mediated immune suppression, and metastasis to the brain. STAT3 is overexpressed in gliomas[72] and propagates tumorigenesis by preventing apoptosis and enhancing proliferation, angiogenesis, invasiveness, and metastasis.[73,74] The STAT3 pathway also becomes constitutively active in diverse tumor-infiltrating immune cells, markedly impairing their antitumor effector responses[75] and enhancing the functional activity of immunosuppressive Tregs[76] and myeloid-derived suppressor cells.[77,78] GSCs also depend on the STAT3 pathway, including for their immunosuppressive properties.[7,79,80] Given that STAT3 is a molecular hub of both tumor-mediated immune suppression and tumorigenesis, it is not surprising that inhibition of this target ranked very highly as a novel therapeutic strategy. Because p-STAT3 blockade agents inhibit Tregs,[76] enhance cytotoxic responses,[75] inhibit growth of glioma cancer stem cells *in vitro*,[81] and reverse immune suppression, p-STAT3 inhibitors have the potential to further enhance peptide-based vaccination strategies, such as with the PEP-3-KLH/CDX 110 vaccine, possibly including patients with bulky tumors who are unable to undergo surgical resection. Although STAT3 is widely recognized as a highly desirable therapeutic target, small molecule inhibitors have been problematic for lack of specificity and associated toxicity leading to discontinuation as therapeutics.[82] The clinical trial implementation of another STAT3 inhibitor, WP1066, was delayed secondary to poor water solubility, which has recently been solved by using it in a spray-dried nanoparticle formulation (SDD1).[83] The preclinical data available for WP1066 are sufficiently compelling to justify considering its use in human clinical trials.

The fourth highest-scoring preclinical approach employed an EGFRvIII-CD3 bispecific monoclonal antibody construct. In order to promote an antitumor immune response, bispecific antibodies simultaneously bind to receptors on the surface of immune effector cells and to transmembrane molecules on the surface of cancer cells. An EGFRvIII-CD3 bispecific monoclonal antibody construct (bscEGFRvIIIxCD3) has shown efficacy, specificity, and potency *in vitro* and *in vivo*.[84] Upon binding to both targets, the construct resulted in potent tumor cell lysis, T-cell proliferation, secretion of Th1-type cytokines, and upregulation of T-cell activation markers. Systemic administration produced complete cures in up to 75% of mice with established EGFRvIII-expressing intracerebral tumors, while no effect was observed among those with intracerebral tumors lacking EGFRvIII expression.[84] Formal toxicity studies of this agent are currently underway in preparation for clinical trials, with no apparent toxicity detected to date.

Ranking equivalently as the EGFRvIII-CD3 bispecific monoclonal antibody construct, the fourth highest-scoring preclinical agent was also the IDH1 peptide vaccine. *IDH1* mutations, specifically at the R132H site, are present in most low-grade gliomas and define secondary GBM.[85] Although found in approximately 12% of GBMs, IDH1 mutations may drive the progression of a lower grade tumor to GBM.[86] An IDH1(R132H) peptide vaccine has recently been developed and has been shown to induce a specific antitumor immune response against *IDH1(R132H)*-mutated tumors in an MHC-humanized animal model.[87] Moreover, it has been shown that targeting the *IDH1(R132H)* mutation in an intracranial glioma model system can significantly prolong survival, with a cure rate of 25%.[88] There is an active phase I trial underway evaluating the IDH1 peptide vaccine in *IDH1(R132H)*-mutated grade III-IV gliomas.

Therapeutic agents without an antigenic target score lower

Approaches lacking an antigenic target such as anti-IL-2Rα, arginine, NK/LAK cellular therapy, 4-1BB aptamers, Adv-TK + Adv-Flt3L, and IL-12 adenoviral therapy had a lower priority score overall. Given that systemic IL-12 therapy can be toxic, mutant herpes simplex (HSV) vectors expressing IL-12 for gene therapy have been developed.[89-92] IL-12 has potent antitumor properties, possesses antiangiogenic properties, and enhances the cytolytic activity of NK cells and CTLs. IL-12-secreting HSV has shown antiglioma immune activity in a murine glioma model,[89,91] and has been shown to be safe in a non-human primate model.[93] Phase I trial results with this agent in human breast cancer have been acceptable,[94] and this modality is currently being evaluated in a phase I clinical trial in GBM (NCT02026271). Adv-TK + Adv-Flt3L, a combinatorial gene mediated immunotherapeutic strategy, utilizes the genes for Fms-like tyrosine kinase 3 ligand, which attracts DCs, and thymidine kinase. This strategy, with ganciclovir treatment, has been shown to prolong survival and shrink intracranial tumors in murine models.[95,96] A phase I clinical trial utilizing this combined gene immunotherapeutic strategy is currently recruiting patients harboring resectable primary GBM (NCT01811992). Although CTLA-4 inhibition does not have an antigenic target, as CTLA-4 expression is restricted directly to T cells, this therapeutic actually ranked highly, given its immune activation/effector response, preclinical, and clinical scores.

Therapeutic agents without immune activation and effector response properties score lower

TGF-β antisense compounds, anti-IL-2Rα, NK/LAK adoptive cellular therapy, and IDO inhibitors all ranked lower. Each of these agents had a priority score of 0 in the immune activation and effector response category, as there is no published evidence to date that any of these agents activate an immune response, induce immune trafficking to the tumor, and/or maintain an effector response within the tumor. Although neutralizing TGF-β has been shown to result in an enhanced immune effector response,[97] traberderson, an antisense phosphorothioate oligodeoxynucleotide, has not been shown to activate or maintain an immune effector response *in vivo*.

Arginine, 4-1BB aptamers, Adv-TK + Adv-Flt3L, and IDO therapies show the lowest scores of the preclinical agents

Considering that arginine-based therapy, Adv-TK + Adv-Flt3L, and 4-1BB aptamers do not have a dedicated antigenic target, and that IDO therapy has not been shown to activate or maintain an immune response (Table 3), these therapies had the lowest priority scores. Both IDO inhibitors and arginine-based therapies are in initial phase I clinical trial testing in GBM, and if there is a favorable safety profile, they could be considered in combination with T-cell-enhancing therapies and antigen-targeted approaches. Of course, with additional emerging data, the relative merits of a given approach to others would be expected to change.

Discussion

In many instances, agents/approaches such as CDX 110 and DCs that are most advanced in clinical trials demonstrate the highest priority score. Although the EGFRvIII peptide vaccine scored well in the clinical category, other tumor-specific or tumor-associated antigens are being targeted such as cancer-testes antigens, tumor-differentiation antigens, viral-related antigens, or mutated oncogenic proteins. EGFRvIII is a driver of gliomagenesis, and it is not clear whether the other targets will elicit similar responses. The peptides selected for cancer vaccines are typically short, around 9 or 10 amino acids long, and are capable of binding to MHC class I molecules, which leads to activation of cytotoxic T cells. It is unclear whether individual peptides or whole tumor lysates induce a better immune response, as they have never been studied head to head. However, these alternative approaches may provide distinct advantages by treating more than a select subset of GBM patients (as is the case for CDX 110) or targeting a greater percentage of the tumor's cells, as EGFRvIII staining is isolated and heterogeneous.

In the DC strategy, immune responses have also been demonstrated with the use of surrogate endpoints. In patients who underwent reoperation after vaccination with DCs, some have had infiltration of CTLs within the tumor.[35,40,98] The priority score here has benefited from the recent findings of Mitchell *et al.*,[22] showing the presence of extreme responders (>40 mo survival); however, this was a small group of patients and required preconditioning of the vaccine site with tetanus/diphtheria (Td) toxoid, a potent recall antigen. Moreover, the antigenic target here was CMV pp65, which has also been used in the setting of adoptive T-cell immune therapy.[22]

Ultimately, we predict that therapeutic approaches that activate the immune response, induce trafficking to the tumor, and maintain effector function will most likely be of clinical benefit. An example of this strategy would be a peptide vaccine (providing an immunogenic target) combined with an antibody that triggers costimulation plus an immune checkpoint inhibitor. Alternatively, patients could be selected who have a tumor that elaborates immune-attracting chemokines or be treated with an agent that induces this tumor property. For example, the TLR3 agonist poly-ICLC significantly enhances the homing of peptide vaccine-induced CTLs to the glioma site via induction of relevant chemokines in mouse glioma models.[99,100] Moreover, use of proinflammatory cytokines (such as IL-12, IL-7, and IL-15), activating antibodies to costimulatory molecules (such as CD40), or blocking antibodies to immune inhibitory cytokines (such as IL-10 or TGF-β) could all potentially enhance clinical activity. The lack of therapeutic effect of many prior immunotherapy tactics, such as the use of poly-ICLC and TLR agonists,[101-103] is probably related to the fact that only one essential component of the antitumor immune cascade was addressed. However, combinatory use of these agents with other therapeutic approaches is actively being evaluated.

One of the more surprising findings was the relatively lower score of the heat shock protein (HSP) vaccine. This vaccine is generated by purification of HSP from the resected GBM, with subsequent reinfusion of the complex to allow the chaperone to interact with antigen-presenting cells (APCs), thus priming the

lymphocytes with a varied cohort of antigenic peptides. However, the score was influenced by the absence of *in vivo* preclinical glioma models supporting its use and failure to demonstrate therapeutic efficacy in phase III clinical trials with other solid malignancies.[13,14] Nevertheless, ongoing clinical trials are using lymphodepleting regimens that may influence its therapeutic profile. Additionally, clinical trials in patients with recurrent GBM have shown that this treatment elicits both adaptive and innate immune responses, is well tolerated, and may improve survival when compared with historic controls.[104,105] One caveat regarding such conflicting data is whether treatment failure in phase III clinical trials with other malignancies should be used to penalize an approach in GBM. If so, to what degree? Certainly most clinical trials evaluating DCs have not been efficacious in other types of malignancies.[106-108] Similarly, there is a paucity of preclinical studies evaluating oral arginine in GBM, even though arginine has been shown to enhance immunotherapy in other preclinical tumor models.[109,110] However, given that such an agent is cost effective and nontoxic, this therapy is currently being investigated in a phase I clinical trial in GBM

Areas that merit additional investigation include small molecule inhibitors and those agents that target the innate immune system. Blocking M2 polarization with the inhibitor CSF-1R has been shown to suppress glioma growth.[58] A small molecule inhibitor of CSF-1R, PLX3397, is currently being tested in patients with solid malignancies (NCT01346358, NCT02452424). STAT3 blockade agents have multiple mechanisms of activity, including direct tumor-cytotoxic effects and the ability to overcome the negative modulatory effects of the local tumor microenvironment, allowing for immunological recognition and clearance of cancer cells, including stem cells.[111-113] Thirdly, agents that target the innate immune system has overall lower scores; yet, in the case of GBM patients that have little antigenic expression, innate immune therapeutic strategies, such as adoptive NK treatment, may actually have a benefit.

Even though the score card is dynamic and updatable, it has certain limitations. A key one results from the limited proprietary information offered by pharma, which can result in an artificially low priority score. Additionally, the accuracy of the reported data and the cut-off points for several of these categories may be arbitrary. For example, there is no perfect single preclinical model system that is appropriate for GBM research, as xenograft use is limited due to a compromised host immune system, some preclinical tumor models may be more difficult to treat than others, and the obvious variation of different lab protocols, experimental designs, etc. Indeed, spontaneous tumors in immunocompetent murine models (i.e., GL261, GEMMs, VM/Dk, etc) are the most applicable to the human behavior and nature of these tumors at this time, and provide a promising avenue for studying immunotherapy and immunosuppression in this horrible disease.[114] Even so, their use is also limited due to reproducibility, labor intensive procedures, latency of tumor formation, and cost. Unfortunately, the scoring system is not sensitive enough to take all of these differences into account. Moreover, a therapeutic that has an antigen target (EGFRvIII) is given more weight in the score card than a therapeutic that does not (IL-12); these agents instead may be associated with a variety of other mechanisms of potential antitumor immunoreactivity. The expression of antigens and other immune targets can also be quite inducible after various immunotherapeutic interventions (i.e., IFN-gamma induces PD-L1 expression).[115] Therefore, if there is a defined antigen, should a clinical trial be penalized if it does not use it for stratification/eligibility consideration? So, the reservation exists that the scoring of antigen targets and other molecular targets within the same scoring system may not be entirely appropriate.

Also, the score card does not take into account the overall mutational and neoantigen load. Using precision medicine to target the genetic features of a malignancy is an exciting subject in oncologic immunotherapy. For example, overall mutational load, neoantigen load, and expression of cytolytic markers in the immune microenvironment are associated with clinical response to immune checkpoint inhibitors (e.g., anti-CTLA-4, anti-PD-1/PD-L1 antibodies) in melanoma and non-small cell lung carcinoma.[116-118] The accumulation of somatic mutations in GBM could possibly improve the response to such therapies as well, and including high mutational burden as a "target" could be considered in the score card.

Moreover, the current analysis was confined to published works and clinical trials listed on www.clinicaltrials.gov, but it did not include a variety of historical or unpublished studies. For example, there have been several cytokine stimulation approaches, such as with IL-2, that have been studied in a variety of cancers. Although IL-2 has been used successfully in the treatment of melanoma and[119] renal-cell cancer,[120] it has not shown benefit in GBM (unpublished data, personal communication from Dr Elizabeth Grimm), and thus was not included. Similarly, TLR agonists were also not included. TLRs are pattern-recognition receptors whose activation initiates innate and adaptive immunity. The potent immunostimulatory properties of TLRs and their associated ligands have been utilized as an immunotherapeutic strategy for cancer therapy, including with glioma.[121] To date, three clinical trials of TLR agonists/poly-ICLC in GBM have been completed, with marginal improvement in survival.[101-103] However, they may have activity when combined with other immunotherapeutic agents, as shown in other clinical trials.[31,122,123] Moreover, the score card did not include agents in phase I clinical trials in GBM without any published preclinical/clinical data in this disease process: these include the multipeptide vaccines (ICT107, SL-701, IMA950 in which the clinical trial was terminated), and some of the personalized approaches (GAPVAC, Neovax, ERC1671, ADU-623, TRC105). As more data becomes available on these approaches, these can certainly be added to the score card, which is dynamic and updatable.

Another major limitation is the way in which the DC strategies were amalgamated. Given that there are multiple DC strategies (use of tumor lysates, cell fusions, RNA, peptides) with different antigen targets (CMV pp65, EGFRvIII, HER2, gp100, etc.), all of them were combined in one column in the score card for the sake of simplicity in presentation. However, this approach may require its own separate score card, including HLA-typing requirements, for patients who are capable/willing to travel to a specialized center that manufactures these therapies. Moreover, the score card prioritizes the presence of extreme responders, but it is challenging to reconcile if extreme

responses are due to selection bias, other factors unrelated to the therapeutic in question, or the actual therapeutic. Most importantly, the criteria chosen to score these therapies have not been validated as being predictive of the ultimate efficacy, marketability, or adoptability of a given therapeutic approach in oncology.

Finally, the score card does not include categories for cost effectiveness and global practicality given that exact cut-points for these categories are not feasible; however, these categories should be considered in a global adaptive Bayesian clinical trial.[2] In general, an agent that can be industrially manufactured (i.e., a small molecule inhibitor or an antibody) is fairly inexpensive to produce; on the other hand, cellular products like DCs cost significantly more to produce per patient. The caveat here is that although antibody therapies may be relatively inexpensive to produce,[124] the cost per patient may not reflect this reality.[125] Practicality, such as off-the-shelf strategies, for global use relates to the ability to implement the immunotherapeutic strategy internationally or in community hospital settings. As patients with GBM may have mobility limitations, therapy at a local cancer community center may be more convenient for some patients. Therefore, commercially available agents would potentially score higher in these categories. Cell-based therapies would score lower in these categories because cellular immune therapeutics are patient-specific, uniformity of the therapeutic products is likely to vary, and they pose a greater regulatory hurdle. Most patients do not have access to the specialized medical centers necessary to produce and administer cell-based therapies, and even among these, complex cellular processing approaches are limited and not uniform. Because of the time and processing required to generate the product, the cost will be significantly higher. Ultimately, determining a therapeutic benefit to cost ratio (i.e., extended months of survival/cost) for each strategy could further refine a score for this category and may justify more labor-intensive strategies.

The score card may also provide guidance for go/no-go translational developmental efforts. For example, if the antigen/target score is >5 or the immune activation/effector score is >2, then the agent could go to therapeutic development. If the preclinical score is >7, then the agent goes to phase I clinical trials. If the clinical score is >4, then the agent goes to phase II clinical trials. Notably when the PD-1 and PD-L1 agents were evaluated with the score card in the context of the preclinical melanoma data, the total target, immune activation, and preclinical score was 13—similar to the score of these agents in glioma. Ultimately, these checkpoint inhibitors were approved in melanoma but there are too few immunotherapy examples to definitively define cut points for continued development and clinical trial implementation.

The score card can also be updated as new data becomes available. The authors propose a few alternatives to how this can be implemented. One method includes crowdsourcing the information by neurosurgeons, neuro-oncologists, pathologists, basic and clinical neuroscientists, etc., where information can be entered "online" into a live database as new data becomes available on immunotherapeutics. The other alternative is to have uninterested parties review the literature periodically to update the score card as new data becomes available. One other alternative includes having an expert committee to review the literature periodically and update the score card.

In summary, one of the more promising strategies for the treatment of gliomas is immunotherapy. Recently, there has been much excitement regarding the immunotherapeutic agents advancing into clinical trials. The authors propose a prioritization method for evaluating the immunotherapeutic drugs available. This prioritization score card, which includes published evidence, is based on what the authors believe are the key features defining a successful immunotherapeutic tactic, providing a rational method of evaluating immunotherapies. Ultimately, we hope that this score card will be a useful tool for providers, so that they will be better informed and hence better equipped to advise and serve this challenging patient population.

Disclosure of potential conflict of interest

ABH has received research grants from Merck, has been a paid consultant for Bristol Myers Squibb, and receives licensing and royalty fees from Celldex Therapeutics. HO has inventions exclusively licensed to Stemline Therapeutics, Inc. and to Intrexon.

Acknowledgments

Special thanks to David M. Wildrick, Ph.D. and Audria Patrick for their editorial and administrative support.

Funding

This study was funded by The Dr Marnie Rose Foundation, the Ben and Catherine Ivy Foundation, The University of Texas at MD Anderson Cancer Center GBM Moonshot Program, and the National Institutes of Health grants CA1208113, P50 CA127001, and P30 CA016672.

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