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Review article

Translational gap in ongoing clinical trials for glioma

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ABSTRACT

Despite the vast amounts of information gathered about gliomas, the overall survival of glioma patients has not improved in the last four decades. This could partially be due to an apparent failure to include basic concepts of glioma biology into clinical trials. Specifically, attempts to overcome the limitations of the blood brain barrier (BBB) and the chemoresistance of glioma stem cells (GSCs) were seldom included (a phenomenon known as the translational gap, TG) in a study involving 29 Phase I/II clinical trials (P2CT) published in 2011. The aim of this study was to re-evaluate this finding with a new series of 100 ongoing, but still unpublished, P2CT in order to determine if there is a TG reduction. As indicators, we evaluated in each P2CT the number of drugs tested, concomitant radiotherapy, and the ability of drugs to pass the BBB and to target GSCs. Compared to clinical trials published in 2011, we found that while in OCT there is an increase in the number of P2CT using two drugs (from 24.1% to 44.9%), and an increase in the number of drugs able to pass the BBB (7.14% versus 64.29%) and target GSCs (0% versus 16.3%), there was a decrease in the number of P2CT using concomitant radiotherapy (34.5% versus 18.37%). Overall our results suggest that there is only a modest improvement regarding reducing the TG because the vast majority of ongoing P2CT are still not including well known concepts of glioma biology important for a successful treatment.

1. Introduction

Gliomas are some of the most aggressive brain tumors, and despite the vast amounts of research and resources allocated to find a cure, there has been a lack of progress in improving the survival of cancer patients. The prognosis for glioma patients is exceptionally low, especially for glioblastoma multiforme (GBM), the most common form of glioma in humans. Currently, the standard treatment for patients with GBM involves surgery, followed by radiotherapy and the administration of Temozolomide (TMZ). In the best scenario, this treatment only extends patient survival by about 22 months, but only for a select few individuals whose tumor contained a methylated MGMT promoter [1]. The average median survival time for GBM ranges from 12 to 16 months [2].

Gliomas, like most solid tumors, contain a subpopulation of cancer-stem like cells (GS-LCs) that have been associated with chemoresistance and tumor relapse [3]. GS-LCs have been isolated in 2003 and 2004 [4,5], and are known to be resistant to Temozolomide and other conventional anticancer drugs [6–8], partially explaining the poor success of current treatments.

Another factor that has limited glioma treatment success is the blood brain barrier (BBB), which prevents the diffusion of anticancer drugs into the central nervous system [9]. It is expected then that newly developed therapeutic interventions should take in consideration these two factors, which have been known for decades to impact the outcome of clinical trials. However, by analyzing 29 clinical trials published during 2011, we found an important "translational gap" in glioma research: our study provided evidence supporting that there was no attempt by the sample clinical trials to utilize drugs that target GSCs in 2011, and only two of the twenty-nine studies published in 2011 included attempts to overcome the limitation imposed by the BBB. This lack of information translation results in repeated treatment failures, and will continue to be a significant waste of time and resources for researchers if the translational gap is not eliminated or reduced. In this study, we have analyzed about 100 ongoing (but still not published) clinical trials in order to evaluate if there has been an improvement in the design of glioma clinical trials regarding the translational gap.

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Table 1
List of 100 ongoing Phase I/II and II Glioma Clinical Trials collected from www.clinicaltrials.gov by searching "phase II gliomas" and refining the study results to "Interventional Studies," the "Adult" age range, "Completed" studies "With Results," and "Phase II."

Result #	Clinical trials ID	Condition/type of glioma	Participants	Drug (s)	Age (groups)	BBB	GSC targeting	RT	Other intervention	Endpoints	Start date	Duration in months (end date)
1	NCT00047879	Recurrent	7	Pegylated Interferon Alfa 2b + Thalidomide	18+ (Adult, Senior)	Pegylated Interferon Alfa 2b: NK; Thalidomide: NK	Pegylated Interferon Alfa 2b: NK; Thalidomide: NK	No	No	PFS	2002	84 (2009)
2	NCT01663012	Bevacizumab-Resistant, High Grade, GBM, AA, AO	20	Etirinotecan pegol/ NKTR-102	18+ (Adult, Senior)	Yes	No	No	No	PFS	2012	36 (2015)
3	NCT00036569	Diffuse Intrinsic Pontine	32	Pegylated Interferon Alfa 2b	up to 21 (Child, Adult)	NK	NK	No	No	2YS, MTTP	2002	120 (2012)
4	NCT00611325	Recurrent, Malignant, GB, GSC	56	Avastin/Bevacizumab + Bortezomib	18+ (Adult, Senior)	Avastin/ Bevacizumab: No; Bortezomib: Yes	Avastin/ Bevacizumab: No; Bortezomib: No	No	No	6mPFS, MPFS, OS	2008	60 (2013)
5	NCT00995007	Recurrent, High Grade, GBM, GSC, AA, AO, AMO	112	ZD6474/Vandetanib +/- Carboplatin	18–100 (Adult, Senior)	ZD6474/ Vandetanib: No; Carboplatin: NK	ZD6474/ Vandetanib: NK; Carboplatin: No	No	No	6mPFS, OS	2009	72 (2015)
6	NCT00615927	Recurrent, Progressive, Grade II, Low Grade, GB, GSC	64	Imatinib Mesylate + Hydroxyurea/ Hydroxycarbamide	18+ (Adult, Senior)	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: Yes	Imatinib Mesylate: No; Hydroxyurea/ Hydroxycarbamide: NK	No	No	12mPFS, MPFS, OS	2006	72 (2012)
7	NCT00727506	Recurrent, Malignant	151	BIBW 2992/Afatinib +/- TMZ	18+ (Adult, Senior)	BIBW 2992/ Afatinib: Yes; TMZ: Yes	BIBW 2992/ Afatinib: NK; TMZ: No	No	No	6mPFS, OBR	2008	96 (2016)
8	NCT00387790	Pontine	64	Motexafin Gadolinium/Xcytrin	Up to 21 (Child, Adult)	No	NK	Yes	No	EFS, OS	2007	36 (2010)
9	NCT00900757	Malignant	57	PALO + TMZ	18–90 (Adult, Senior)	PALO: NK; TMZ: Yes	PALO: NK; TMZ: No	Yes	No	Change in FLIE Score From Baseline – Each Week of RT and TMZ Treatment	2009	36 (2012)
10	NCT00085540	AO, AA, Recurrent, GSC, Giant Cell GB	50	FR901228/ Depsipeptide/ Romidepsin	18+ (Adult, Senior)	NK	NK	No	No	6mPFS, OBR	2005	48 (2009)
11	NCT00501891	GBM	32	Avastin/Bevacizumab + TMZ	18+ (Adult, Senior)	Avastin/ Bevacizumab: No; TMZ: Yes	Avastin/ Bevacizumab: No; TMZ: No	No	Metronomic treatment (TMZ)	6mPFS, OBR, Incidence/Severity of CNS/Systemic Hemorrhage	2007	24 (2009)
12	NCT00275002	Brain/CNS Tumors, Recurrent, Progressive	41	O^6-Benzylguanine + TMZ	Up to 21 (Child, Adult)	O^6-Benzylguanine: Yes; TMZ: Yes	O^6-Benzylguanine: Yes; TMZ: No	No	No	OBR, # of Patients with Grades 3 to 4 Adverse Events (Possibly Related to O^6-Benzylguanine + TMZ)	2006	48 (2010)
13	NCT00392171	GB, AC, OLDG	120	TMZ	19–70 (Adult, Senior)	Yes	No	No	Continuous 28-day Therapy (Patient who failed Conventional 5-day)	6mPFS	2006	36 (2009)
14	NCT00369590	AA, AO, Giant Cell GB, GSC, Recurrent	58	VEGF Trap/Ziv-aflibercept	18+ (Adult, Senior)	NK	NK	No	No	6mPFS, OS, PFS, Safety Profiles	2006	72(2012)