

Paths for improving bevacizumab available in 2018: the ADZT Regimen for better glioblastoma treatment.

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Abbreviations:

apremilast, bevacizumab, dapson, zonisamide, telmisartan, ADZT Regimen; carbonic anhydrase, CA; cyclic adenosine monophosphate, cAMP; carbonic anhydrase, CA; cerebrospinal fluid, CSF; phosphodiesterase 4, PDE4; vascular endothelial growth factor A, VEGF;

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Running title:

The ADZT Regimen for glioblastoma.

Abstract. [132 words]

During glioblastoma treatment, the pharmaceutical monoclonal antibody to VEGF, bevacizumab, has improved quality of life and delayed progression for several months but has not, or only marginally prolonged overall survival. In 2017 several dramatic research papers appeared that are crucial to our understanding of glioblastoma vis a vis the mode of action of bevacizumab. As a consequence of these papers, a new, potentially more effective, treatment protocol can be built around bevacizumab. This is the ADZT Regimen where four old drugs are added to bevacizumab. These four are apremilast, marketed to treat psoriasis, dapsone, marketed to treat Hansen's disease, zonisamide, marketed to treat seizures, and telmisartan, marketed to treat hypertension. The ancillary attributes of each of these drugs has been shown to augment bevacizumab. This paper will detail the research data supporting that contention.

1. Introduction.

This paper presents the physiological basis of the ADZT Regimen, a new proposed augmentation strategy to improve bevacizumab (Avastin™) effects during treatment of glioblastoma. Bevacizumab is a monoclonal pharmaceutical antibody directed against vascular endothelial growth factor A (VEGF). Initially FDA and EMA approved to treat some forms of macular degeneration, it is now also approved for, and commonly used during glioblastoma treatment after resection, radiation, and temozolomide. Initial clinical studies in glioblastoma showed that bevacizumab delayed time to progression, ~ 10 versus ~ 7 months, but no significant difference in overall survival of ~ 16 months [1]. Others found similar results [2]. Newer bevacizumab regimens with 100 mg/m²/day cycles of temozolomide and newer studies of lower bevacizumab doses have indicated some survival benefit [3]. Glioblastoma has been an unusually treatment refractory cancer, justifying our exploration of unproven but low risk regimens like ADZT.

Multiple clinical trials have attempted, yet failed, to augment bevacizumab in prolonging overall survival. For example in 2017 alone, clinical studies adding vorinostat, a histone deacetylase inhibitor [4], adding lomustine [5], adding onartuzumab [6], all failed to prolong survival.

Crucial papers appeared in 2017 on the physiology of bevacizumab, each giving new data, each independently converging on potential improvements to bevacizumab treatment. By using these four older drugs that are available now (mid-2018) we might be able to exploit these new insights to improve bevacizumab's effectiveness in treating glioblastoma. The 2017 papers are coalesced and integrated to form the ADZT Regimen outlined here.

The four drugs of ADZT Regimen are apremilast - an anti-psoriasis drug, dapsone - an antibiotic, zonisamide - an anti-seizure drug, and telmisartan, marketed to treat hypertension. Four are cheap, generic, widely available drugs, the fourth, apremilast remain proprietary and somewhat expensive. The ancillary attributes of each and the physiology of their interactions with bevacizumab's effects are detailed below. None of the ADZT drugs are

currently FDA or EMA approved or marketed for use in augmentation of bevacizumab.

2. Apremilast.

Introduced to clinical practice in 2004, apremilast is a 461 Da, selective phosphodiesterase (PDE) 4 inhibitor. There are over a dozen currently recognized isoforms of PDE. The problem with some past studies of pan-PDE inhibitors like pentoxifylline was that some PDE inhibitors have substrates that result in opposite intracellular effects to other PDE inhibitors. Since PDE4's predominant intracellular role is in catalysing reaction cyclic adenosine monophosphate (cAMP) to AMP, apremilast results in increased intracellular cAMP. cAMP is synthesized by ATP conversion to cAMP mediated by adenylate cyclase. Multiple pro-inflammatory cytokines are partially inversely controlled by intracellular cAMP levels [7, 8]. As intracellular cAMP decreases, synthesis and release of TNF-alpha, IL-2, IL-8, and interferon-gamma tend to increase [7, 8].

In accord with these theoretical considerations, at 20 mg twice daily apremilast reduced IL-6, IL-8, MCP-1 and TNF-alpha in people being treated for psoriasis or psoriatic arthritis [8, 9]. Since these cytokines also have been shown to participate in glioblastoma growth facilitation we might expect benefit from apremilast on this basis alone.

Apremilast is now being used to successfully treat psoriasis [9-11] and psoriatic arthritis [12], atopic dermatitis [13], lichen planus, Behçet disease [14], ankylosing spondylitis [15], discoid lupus [16], chronic cutaneous sarcoidosis [17] and other inflammatory dermatoses.

Apremilast is generally well tolerated with mild nausea, diarrhea and headache being the most common side effects. Discontinuation due to side effects was 5% with placebo, 7% with apremilast [12]. Another PDE4 specific inhibitor, rolipram, was investigated in the 1980's as an antidepressant but development stopped due to excessive nausea [18]. Rolipram inhibited growth of A172 and U87MG glioblastoma cell lines by a PDE4 mediated path [19].

In March 2017 Ramezani et al published a crucial paper for our next step in improving glioblastoma treatment by improving effectiveness of bevacizumab [20]. They showed that adding a PDE4 inhibitor, rolipram, to bevacizumab enhanced in vitro cytotoxicity and reduced free VEGF in the culture medium compared to bevacizumab alone. This finding makes sense in the larger context of pro-inflammatory cytokine release generally.

Understanding that VEGF action might also be inversely related to intracellular cAMP opens several exciting augmentation paths by which we might make bevacizumab more effective in treating glioblastoma. Alternatively, diminished free VEGF after rolipram could be a secondary effect of previously established reduction of TNF-alpha, IL-8 and other cytokines by PDE4 inhibition.

So PDE4 inhibitors have evidence of a) augmentation of bevacizumab effects and independent of that, b) anti-glioma growth effects, and c) lower synthesis of inflammation-related cytokines secondary to increased intracellular cAMP.

Apremilast would be a low-risk addition to bevacizumab.

3. Bevacizumab

Introduced clinically in 2004, bevacizumab is commonly called an anti-angiogenic agent, but it should be more accurately termed what it simply and literally is - a monoclonal humanized antibody to soluble VEGF. Beyond direct vessel effects, bevacizumab strongly suppressed glioblastoma cell expression of 130 kDa platelet endothelial cell adhesion molecule and slightly reduced proliferation but upregulated matrix metalloproteinase-2 production [20]. Also, for example, bevacizumab is cytotoxic (in vitro at least) to VEGF synthesizing glioblastoma cells by binding to outer cell membrane bound VEGF [21].

When a glioblastoma progresses while on bevacizumab, survival is under half a year [22-24]. Performance status and quality of life usually improve with

bevacizumab but often overall survival does not. ADZT aims to address this discrepancy.

Distorted, flawed vessels are common in glioblastoma. Pruning of these pathologic vessels occurs during bevacizumab treatment with consequent reduction of tumor-related brain tissue edema [24]. But an interesting paradox occurs here - vessel density and vessel morphological and functional abnormality decrease under bevacizumab treatment, yet hypoxia seems to increase [25].

4. Dapsone.

Introduced in the mid-1940's, dapsone is a 248 Da sulfone antibiotic still in wide use. In addition to antibacterial activity in treating Hansen's disease and pulmonary tuberculosis, dapsone has anti-protozoal effects and is used currently in treating Plasmodia infections. Unrelated to antibiotic activity, dapsone has found some utility in treating neutrophilic dermatoses like bullous pemphigoid, dermatitis herpetiformis, and others [33] including the neutrophilic rash caused by epidermal growth factor receptor inhibiting drugs [34, 35]. In a series of six papers my colleagues and I have amply documented the rationale for using dapsone to deprive the tumors of neutrophil-delivered VEGF during the treatment of glioblastoma [36-38].

As predicted in 2015 and in 2016 [34, 35], dapsone was shown to ameliorate anti-epidermal growth factor receptor mediated rash in 2017 [39, 40], a rash mediated by VEGF containing neutrophils drawn to rash areas by IL-8 during erlotinib or cetuximab treatment but countered by dapsone. We therefore expect dapsone to augment bevacizumab by reducing neutrophil borne VEGF to glioblastomas.

Dapsone has some in vitro anti-glioma activity on its own [41].

6. Zonisamide

Introduced in 1993, zonisamide is a 212 Da anti-seizure drug with carbonic

anhydrase (CA) inhibitory activity that also blocks voltage-sensitive Na⁺ channels and T-type Ca⁺⁺ channels [42, 43]. There are a dozen CA isoforms. In vitro, the CA IX K_i of zonisamide is 5.1 nM [44]. Zonisamide, unique among anticonvulsants, also inhibits monoamine oxidase [45].

CA catalyses reversible hydration of carbon dioxide to bicarbonate and a proton ($\text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{HCO}_3^- + \text{H}^+$). Of the many isoforms of CA active in cancer physiology, CA IX is particularly prominent, including in glioblastoma [46-48]. CA IX resides on the outer cell membrane's exterior. The resulting bicarbonate ion is imported by various pumps such as the Na⁺/HCO₃⁻ cotransporter, raising intracellular pH but lowering extracellular pH as the proton remains extracellular. This is one of the primary mechanisms generating cancer's [49] - and specifically glioblastoma's - abnormal extracellular acidic milieu.

Concordant with above mechanism of cancer-related extracellular acidification, topiramate, an anti-seizure and CA IX inhibiting drug similar to zonisamide, increased glioblastoma intracellular pH [50].

An immunohistochemistry study of grades II, III and IV glioma biopsy tissue by Yoo et al found respectively 21%, 33% and 79% having strong CA IX expression [48]. Degree of CA IX expression inversely correlated with survival in this and in other similar studies [48, 51]. Higher CA IX expression facilitates more vigorous in vitro growth of glioblastoma cell lines [52]. In clinical disease, differential survival of glioblastoma patients with high CA IX expression - 0 of 9 surviving a year - versus those with low CA IX expression - 9 of 34 patients surviving a year [52] - would alone seem to justify a clinical trial of already-marketed and well-tested CA IX inhibitors like acetazolamide, topiramate, or zonisamide.

In light of that inverse correlation, conversion of a high CA IX expression glioblastoma to a poor CA IX functioning tumor by zonisamide may well prolong survival.

Both an experimental CA IX inhibitor or temozolomide individually inhibited growth of human glioblastoma xenografted in nude mice. The effect was synergistic when used together [53]. The FDA approved pan-CA inhibitor acetazolamide augmented temozolomide cytotoxicity to glioma cells in vitro [54].

Acetazolamide reduces production of cerebrospinal fluid (CSF) and is used clinically for this purpose [55], thus forming another potential benefit for use of CA IX inhibitors like zonisamide during glioblastoma treatment, in addition to potential augmentation of bevacizumab.

Dexamethasone use tends to worsen prognosis in glioblastoma [56] but must be used to decrease elevated CSF pressure during the course of glioblastoma. Since we expect dapsone and zonisamide will lower need for steroids we might see overall survival increase on that account as well.

Acetazolamide is a sulfonamide pan-CA inhibitor in continuous clinical use since the 1950's with demonstrable preclinical anti-glioma activity [57, 58] but so far has had no clinical trial in human glioblastoma other than to treat plateau waves [59] as far as I was able to determine. Acetazolamide is currently clinically used to treat mountain sickness, elevated intraocular pressure, and pseudotumor cerebri syndrome [60, 61]. Acetazolamide could be substituted for zonisamide in an ADZT-type regimen.

The use of CA IX inhibition with zonisamide (or acetazolamide) would be a realization of Koltai's "repurposed drug combinations targeting this vulnerable side [i.e. decreased extracellular pH and need to export increased intracellular protons] of cancer development" [62].

Crucially for our intended use of zonisamide, the lower CAIX activity is in a given tumor tissue, the more effective bevacizumab becomes [63-70].

6. Telmisartan.

Telmisartan is an angiotensin receptor blocking drug (ARB) with several

unique features that recommend its use in glioblastoma, and particularly in combination with bevacizumab. ARBs, like angiotensin converting enzyme (ACE) inhibitors, are marketed for a variety of indications, but prominently hypertension. Telmisartan is uniquely lipophilic, has tighter affinity to the angiotensin 2 type 1 receptor, and it happens to inhibit PPAR-gamma as well [71, 72], all attributes useful during treatment of glioblastoma, and particularly in co-administration with bevacizumab.

In 2017 Levin et al suggested adding an ARB or ACE inhibitor to bevacizumab based on their retrospective glioblastoma study showing overall survival of ~ 25 months in those receiving low dose bevacizumab plus an ARB or ACE inhibitor, compared to ~ 14 months for those receiving low dose bevacizumab only [73]. It should be noted here that this inverse dose-response relationship is currently (as of 2018) unexplained and must be a huge hint in our efforts to understand how bevacizumab works.

Also in 2017, Menter et al found similar but slightly different results in non-squamous, non-small cell lung cancer treated with carboplatin and paclitaxel with or without bevacizumab. Bevacizumab prolonged survival, as did an ACEi or ARB, but increased survival by addition of an ACE inhibitor/ARB to bevacizumab did not reach statistical significance for additive effect [74].

A potential added benefit of adding telmisartan is that it is also a PPAR-gamma agonist and PPAR-gamma agonism has significant glioblastoma growth inhibiting effects [75]

In metastatic colon cancer, those receiving bevacizumab with an ARB had longer progression free survival, 8 versus 6 months, and longer overall survival, 26 versus 16 months [76].

7. Conclusions.

This paper outlined past research pointing to potential advantages of adding four older drugs concurrently with bevacizumab. The four drugs - apremilast, dapsone, zonisamide, telmisartan - are low risk drugs when used individually,

are inexpensive, and generally well known and available to physicians worldwide.

Below is a bullet-point list of potential or expected benefits of the ADZT Regimen during the course of glioblastoma:

- Lower ICP.
- Steroid sparing.
- Augment bevacizumab effect.
- Provide synergy with temozolomide.
- Provide inherent anti-glioma effects.
- Individually have low side effects, low risk.

The ADZT Regimen follows other efforts to improve the anti-glioblastoma effects of bevacizumab. Adding the CXCR4 inhibitor plerixafor for example, that did not improve survival over bevacizumab alone, but did provide some clues as to resistance or circumvention pathways around anti-VEGF effects of bevacizumab [77]. As seen in many cancer chemotherapies, exposure of glioblastoma to bevacizumab engages tumor growth enhancing compensatory pathways in addition to the intended growth inhibition [78]. The ADZT Regimen was designed to enhance bevacizumab mediated growth inhibition by blocking several of these circumvention pathways.

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