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REVIEW AND SYNTHESIS ARTICLE

Adding perphenazine to increase effectiveness of standard glioblastoma chemoirradiation

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Summary

In the effort to improve treatment effectiveness in glioblastoma, this short note reviewed collected data on the pathophysiology of glioblastoma with particular reference to intersections with the pharmacology of perphenazine. That study identified five areas of potentially beneficial intersection. Data showed seemingly 5 independent perphenazine attributes of benefit to glioblastoma treatment - i) blocking dopamine receptor 2, ii) reducing centrifugal migration of subventricular zone cells by blocking dopamine receptor 3, iii) blocking serotonin receptor 7, iv) activation of protein phosphatase 2, and v) nausea reduction. Perphenazine is fully compatible with current chemoirradiation protocols and with the commonly used ancillary medicines used in clinical practice during the course of glioblastoma. All these attributes argue for a trial of perphenazine's addition to current standard treatment with temozolomide and irradiation. The subventricular zone seeds the brain with mutated cells that become recurrent glioblastoma after centrifugal migration. The current paper shows how perphenazine might reduce that contribution. Perphenazine is an old, generic, cheap, phenothiazine antipsychotic drug that has been in continuous clinical use worldwide since the 1950's. Clinical experience and research data over these decades have shown perphenazine to be well-tolerated in psychiatric populations, in normals, and in non-psychiatric, medically ill populations for whom perphenazine is used to reduce nausea. For now (Summer, 2020) the nature of glioblastoma requires a polypharmacy approach until/unless a core feature and means to address it can be identified in the future. Conclusions: Perphenazine possesses a remarkable constellation of attributes that recommend its use in GB treatment.

Key words: *dopamine, glioblastoma, perphenazine, protein phosphatase 2A, serotonin, subventricular zone*

Introduction

There has been little progress in treating glioblastoma (GB) since the introduction circa 2005 of temozolomide to the, then standard, resection and irradiation. This paper addresses the rationale for adding perphenazine to current GB treatment. By reviewing recent data on the pathophysiology of GB with specific reference to intersections with the pharmacodynamic attributes of perphenazine, this paper identified five areas of potentially beneficial intersection. Strong empirical evidence for perphenazine's, and related D2 blocking drugs', ability to reduce GB growth is also presented.

Perphenazine is a 404 Da brain-penetrant, cheap, generic drug, approved for use in humans worldwide. It has been in continuous use since the 1950's to treat psychotic states and conditions [1,2]. Perphenazine is also used to reduce nausea [3], or to calm people who are in an acutely disorganized agitated state. It also has adjunctive use in treating depression. Basic pharmacologic parameters of perphenazine are listed in Table 1.

Its antipsychotic properties are thought to be due to blockage of, or inducing reduced activity of, signaling at the dopamine receptor 2 (D2). Per-

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Table 1. Basic pharmacological parameters of perphenazine

Parameters		*References*
Mol. wt.	404 Da, 1 nmol = 404 ng	
Metabolism	CYP2D6, CYP1A2 (minor)	96
Psychiatric dose	4 to 32 mg/d	96
Metabolites	Perphenazine sulfoxide, Dealkyl perphenazine	96
Half-life	~ 10 hours, blood	96, 97
Blood level	1 to 10 nmol/L	98, 99,103
Side effects >5%	day sedation at > 8 mg/day	102
Side effects 1-5%	akathisia, hyperprolactinemia, hypotension, sexual dysfunction	102
Side effects <1%	neuroleptic malignant syndrome	89
psychiatric use	antipsychotic, antidepressant	102
other uses	anti-nausea, antipruritic	84,100,101

Table 2. List of marketed and FDA/EMA approved antipsychotic drugs that have shown anti-glioma effects

Drug	*References*
aripiprazole * #	104, 134
brexpiprazole * #	105
chlorpromazine	106, 107, 108
fluphenazine	109
fluspirilene *	110
haloperidol *	112
metoclopramide	113-115
olanzapine *	116, 117
penfluridol	118-121
perphenazine	22, 63, 79,
pimozide	122, 123
prochlorperazine	22
risperidone *	23, 124,
quetiapine *	125, 126
thioridazine	111, 127, 128,132
trifluoperazine	106, 129-131,133

Remarkably, all 16 block D2 signaling in the brain, albeit with different affinities. All are phenothiazines except for those marked *. Partial D2 antagonist-agonists marked with #. It has not been proven that it is in fact D2 antagonism that is responsible for anti-glioma effect of these drugs

phenazine also exerts inhibitory activity at selected serotonergic (5-HT) receptors that contribute to its adjunctive effects in treating depression. Table 2 lists the currently FDA/EMA approved and marketed D2 blocking drugs used to treat psychosis that, remarkably, all also happen to have a clinical or preclinical research database showing activity in inhibiting glioma growth. The potential for clinical benefit of D2 blockade with approved and marketed anti-psychotic drugs as part of treatment of GB was recently reviewed by four different groups [4-7].

This short paper examined published data on areas of intersection between the documented pharmacodynamic attributes of perphenazine and other marketed D2 blocking drugs generally and what we know about the pathophysiology of GB growth and GB's treatment resistance.

I. GB and dopamine

Human GB biopsy tissue has increased D2 mRNA and protein expression compared to normal brain tissue. The four recent reviews mentioned above discussed in detail many of the pathways by which D2 blocking antipsychotic medicines act to inhibit GB growth [4-7]. D2 blocking also has been discussed as a potential treatment in cancer generally [8-10].

Dopamine signals via 5 different receptors, D1 to D5. Although they each have distinct attributes, they also share certain commonalities. Human GB cells synthesize and secrete dopamine [5]. Signaling at D2 increases GB stem attributes, stimulates growth, and increases their reliance on glycolysis [5]. Perphenazine inhibits both D2 and D3 receptors.

II. GB and need for polypharmacy

1. GB cells use a variety of metabolic energy generation paths that to varying degrees cross-cover for each other [11,12]. Drug repurposing allows use of well-known older drugs that, while not cytotoxic in themselves, are able to block GB survival and growth pathways. GB cells after all, like other cancers, use normal, physiologic growth signals to thrive, albeit abnormally applied.
2. GB like other treatment resistant cancers is a community of mutually supporting subclones [13]. Horizontal communication of resistance exists via double minutes, exosomes, cell fusions, and other means. Disrupting that mutually sup-

porting communication between the subclones, is required for "proper functioning" of the tumor subclones for optimal growth. Thus inhibiting that communication is one path for tumor control.

3. GB's extreme temporal and spatial heterogeneity with multiple cross-covering, growth-driving systems, combined with a uniquely robust motility with consequent wide tissue invasion [14-16] all must be simultaneously blocked - and kept blocked over time - to retard or stop GB growth.

4. Growth driving systems in GB are moving targets, evolving over time and responding to our treatment interventions [17,18]. Also stem cells within a cancer likewise are not a stable clonally related population [19]. Stemness is an attribute that can be lost in daughter cells of stem cells, or gained by daughter cells of stem-marker negative cells [19]. Stemness is a fluid attribute. For these reasons - and the failure over the last 40 years of several hundred clinical GB studies of various cytotoxic drugs or drugs that blocked single growth driving systems - we believe a polypharmacy approach is needed. D2 blocking will be an important part of that polypharmacy for GB.

5. A guiding principle behind the development of more effective GB treatment is the concept used in military planning of clearly identifying and individually addressing the different requirements for A) a main operation, and B) shaping operations (note pleural). The main operation commonly is aimed at destruction of enemy forces. In our case - killing GB cells. Supporting operations are all activities directed at matters peripheral to the main effort, but that are designed to help the main effort succeed. A military example would be destroying a bridge enemy forces might use to bring in reinforcements to where the main operation is occurring.

   In GB treatment this concept must be applied in crafting our treatment regimen. This paper shows how adding perphenazine has five attributes that would qualify it as a worthwhile shaping operation to current main operations of surgery, temozolomide and irradiation.

6. Let the 2011 study in recurrent GB of Hegi et al serve as example of need for shaping operations: In accord with others, they found that 60% of GB had EGFR gene amplification and that agonist stimulation (phosphorylation) of EGFR in vitro resulted downstream phosphorylation of RAS/MAPK and PI3K/AKT pathways. Gefitinib achieved ~ 10 to 20 times higher GB tissue concentrations compared to serum, and effectively prevented EGFR activation (phosphorylation) but had no effect on reducing RAS/MAPK and PI3K/AKT pathways' activation in clinical samples or in a xenograft model. Crucially for our research planning however, they did find effective blocking of downstream RAS/MAPK and PI3K/AKT signaling after in vitro gefitinib exposure [20]. Conclusion from Helgi et al: In vitro GB cell coping paths are not reflective of human disease processes and polypharmacy required to defeat GB's as things now stand.

Elmaci and Altinoz reviewed past data on an old, still-in-use antipsychotic drug, pimozide, and drew the conclusion that it may show GB growth inhibition [21]. Pimozide has similar receptor binding profile as does perphenazine. Pimozide has tighter inhibitory affinity to D2, D3, and calmodulin, but regulatory restrictions in some jurisdictions and risks of EKG QTc prolongation with pimozide would complicate its use in GB. Thus perphenazine.

In addition to the above reasoning, that a polypharmacy approach will be required, we are planning on adding perphenazine to GB treatment based on fully five perphenazine attributes: i) D2 antagonism, ii) D3 antagonism, iii) 5-HT7 inhibition, iv) de-inhibition (i.e. activation) of trimeric protein phosphatase 2A (PP2A), v) nausea reduction. Details on these mechanisms of action and how they therapeutically beneficially interact with GB pathophysiology, with references, follow below:

III. The findings- GB and D2 antagonism

Perphenazine has empirical evidence for anti-GB effects. IC50 of perphenazine to GB cells in vitro was 0.98 μmol [22]. However, this is unlikely to be a relevant mechanism of action though, given the nmol range of clinically achievable levels.

We find the data of Table 2 to be remarkable in that 16 structurally different, marketed, clinically used D2 antagonists should each have evidence of anti-glioma effects. In addition to the autocrine growth loop, the existence of which is suggested by GB's expression of both D2 receptors and dopamine [5] we see strong cytotoxic synergy between temozolomide and D2 blockade [23]. That single empirical evidence alone should be enough to warrant a clinical trial of perphenazine. In addition to the 16 marketed anti-psychotic medicines of Table 2, several experimental, not-yet-marketed D2, D3, and D4 antagonists like Lcc-09 and ONC201 also have demonstrated GB cell killing effects and are being actively pursued for GB treatment [24-26].

Psychosis is one of the most common major malfunctions of humans in all societies worldwide. Because of this, and the general applicability of D2

antagonism in stopping overt psychosis, we have ~ 20 antipsychotic, D2 inhibiting medicines currently marketed in most jurisdictions.

GB spheroid growth in vitro is inhibited by several clinically used D2 antagonists and stimulated by specific D2 agonists [30]. Paths by which D2 antagonism augments temozolomide and other common cancer chemotherapeutic drugs was recently reviewed by Shaw et al, and demonstrated specifically for temozolomide in GB by Liu et al [31,23].

The experimental D2 antagonist, ONC201, has just completed a phase 1 clinical trial in recurrent GB with evidence of good tolerability but little general activity as single agent, although there was one durable remission in an H3K27 mutated case [26].

IV. The Findings- D3 antagonism and the SVZ

Yoon et al early in 2020 distinguished a clear distinction between post-resection GB as originating from centrifugally migrating subventricular zone cells (SVZ) versus recurrences from already present residual cells within brain tissue that had migrated - invaded - brain from the original tumor mass [17]. Collected data below indicate that perphenazine will reduce centrifugal migration of SVZ cells, malignant or non-malignant.

SVZ cells line the lateral ventricles in a ribbon just distal to the hypocellular gap [32]. These SVZ cells are one of the very few areas of the adult brain that give rise to new neurons. Robust data show that SVZ contributes to GB growth, with strong indications that indeed adult GB tends to originate from a malignantly transformed SVZ cell or cell group [17, 33-42]. Indeed, recent evidence indicates that malignant transformation of nonmalignant cells of the SVZ is the primary initiating event from which the cell of origin many human GBs migrate [17,43,44]. Such cells are particularly resistant to TMZ and irradiation due to an abundance of anti-apoptotic Bcl-2 and Mcl-1 [45]. Normal, nonmalignant neural stem cells residing in the SVZ are highly motile, and exhibit normal migratory patterns reminiscent of Scherer's structures in GB [46]. Contact with the SVZ is a poor prognosis sign independent of the molecular GB subtype [34,47].

The SVZ neurons or neuron-like cells replicate throughout life. They also centrifugally migrate throughout life. Both normal SVZ cells and malignant transformed SVZ GB cells proliferate and centrifugally migrate in response to dopaminergic signals, and particularly, specifically, dopaminergic signals at the D3 receptor [33-38, 40, 48]. Hence perphenazine to inhibit D3 driven contributions to GB from the SVZ.

V. The Findings- blocking 5-HT7

5-HT is remarkable in that all Animalia studied use 5-HT in similar or analogous ways. In both invertebrates and vertebrates, 5-HT tends to potentiate or mitigate neuronal activity rather than to start, stop or trigger a specific behavior [49]. 5-HT tends to exert a behavioral fine-tuning effect from crabs to primates.

Of the dozen or so 5-HT receptors currently recognized, 5-HT receptor 7 (5-HT7) is expressed on GB cells where agonism enhances growth [50-52]. This same finding of growth drive stimulation via 5-HT7 is also found in non-small cell lung adenocarcinoma where 5-HT7 agonism drives proliferation, migration, and invasion [53]. Similar growth stimulation by 5-HT7 was seen in neuroendocrine tumors [54], hepatocellular carcinoma [55], and triple negative breast cancer [56,57]

VI. The Findings- De-inhibition of PP2A

PP2A is a trimeric serine-threonine phosphorylase, with a scaffolding subunit , a catalytic subunit , and a regulatory subunit with multiple subunits isoforms, resulting in over 60 combinations [58,59]. Half a dozen inhibitory peptides are recognized. PP2A dephosphorylates many of the substrates phosphorylated by receptor kinases (examples: c-MYC, AKT, Cdc25, Bax, and GSK3) active in driving cancers' growth [58]. Phosphorylation of PP2A itself can inactivate it. Importantly for use in GB, phenothiazines generally, and perphenazine specifically, activate (de-inhibit) PP2A [59, 60].

So common a finding in various cancers is diminished PP2A activity that subnormal PP2A has been termed "the broken off switch in cancer" [61, 62, 63, 64]. PP2A, as a phosphatase, removes a phosphate from phosphorylated kinases, many of which drive GB growth and many of which become inactivated by such dephosphorylation [65,66]. Advantages of activating (de-inhibiting) PP2A during cancer treatment with kinase inhibitors was recently reviewed by Westermarck et al [67,68].

Multiple cell surface receptor kinases phosphorylate PIP2 to PIP3. PTEN reverses that process, dephosphorylating PIP3 to PIP2.

PIP3 phosphorylates AKT, which itself then becomes an active kinase. Higher level phosphorylated AKT correlates with shorter survival in GB. Upregulation of PI3K/AKT pathway has also been documented in GM stem cells. AKT phosphorylates several growth promoting cytosol targets in GB, thus forming a growth driving signaling node contributing to multiple malignant behaviors of GB [27,28,29]. As an important example, PP2A

dephosphorylates AKT, inactivating it in glioma cells [69,70]. AKT phosphorylation is a central signaling hub in phosphorylation chains upon which growth signals from several receptors converge that are required for GB mitosis entry [71].

PTEN and AKT are so fundamental to the normal functioning of all nucleated cells that straight inhibition of AKT seems less promising than simply calming it down, moderating it, reducing the hyperactivation seen in GB.

Because so many outer cell membrane signaling receptors converge on AKT, effect of blocking one or two of them can leave other receptors to cross cover for the blocked ones (our Nile Distributary Problem).

PP2A dephosphorylates proto-oncogene basic helix-loop-helix transcription factor (MYC) resulting in a more rapid degradation of MYC leaving less time for it to act [72]. MYC is often overactive in driving GB growth [73, 74].

PP2A also dephosphorylates Bax, enhancing its pro apoptosis function [75]. Inhibition of PP2A is required for increasing phosphorylation of Wee1, Myt1, and Cdc25, which are in turn required for mitosis entry [59]. We reason that since perphenazine is widely used around the world to treat psychosis, without evidence of mitosis prevention, that the disinhibition of PP2A it exerts must be only partial or at least partially circumventable.

PP2A dephosphorylation of MYC might also be of interest in immunotherapy of GB and other cancers in that MYC transactivates PD-1 ligand [60]. Dephosphorylated MYC is rapidly degraded so lowering MYC dwell time might thereby lower PD-1 immunoinhibitory function.

Perphenazine has demonstrated tumor growth retarding effects via PP2A activation in lymphoma [76], acute lymphocytic leukemia [77], acute myeloid leukemia [78]. Importance of activating PP2A during GB treatment was recently reviewed [62]. PP2A activating perphenazine derivatives are in active development to treat several cancers and have demonstrated preclinical activity [79,80].

VII. The Findings- Anti-nausea effects of perphenazine

Nausea is common during treatment of GB. Although standard current treatment with irradiation and temozolomide is not highly emetogenic, nausea does occur and does shorten progression free survival when it occurs [81,82]. Perphenazine reduces nausea and has a long history of use for that purpose, dating from the 1960's [83-88]. Perphenazine is used as one of several drugs in modern anti-nausea regimens during chemotherapy particularly when one is aiming for "zero tolerance" [87]. Perphenazine and other D2 inhibiting drugs are non-inferior to the more modern drugs of the 'setron group (like ondansetron, granisetron, etc) [3,88]. Anti-nausea effects of perphenazine are additive with 5-HT3 antagonists, NK-1 antagonists and steroids. Given the distress of even grade 1 or 2 nausea or vomiting, perphenazine's good tolerability, and the multiple potential areas of anti-GB growth effects, a trial of perphenazine 8 mg x 1 hora somni added to standard Stupp chemoirradiation right from day 1 of treatment is warranted.

IX. Potential risks of perphenazine

Side effects from perphenazine tend to be dose related and are not common below 6 mg/day. Parkinsonian signs or symptoms (bradykinesia, akinesia, tremor, diminished motor fluidity), or daytime sedation are progressively more frequently seen as dose exceeds 8-12 mg/day but are fully and rapidly reversible upon dose lowering.

More serious but also readily reversible with medical treatment followed by dose reduction are neuroleptic malignant syndrome (NMS) and serotonin syndrome. Serotonin syndrome is characterized by confusion, autonomic nervous system instability, neurologic manifestations, and hyperthermia. NMS is estimated to occur in three patients per 10,000 patients treated with D2 blocking medicines [89]. NMS is characterized by a similar clinical picture as serotonin syndrome with elevations of creatine kinase, lactate dehydrogenase, aspartate transaminase), and leukocyte count. These two nominal entities can overlap [90-93]. Formes frustes are far more common than the fully blown, classically defined syndromes. Left untreated these can be fatal but when recognized early, treatment with cessation of the offending drug and supportive measures are commonly enough for rapid resolution, although more active reversal medical treatments are available [94].

Tardive dyskinesia is a late adverse effect seen occasionally after decades of any D2 inhibitor's use. Tardive dyskinesia tends to be treatable but irreversible. Perphenazine is one of the four commonly used D2 blocking drugs for which routine drug level monitoring is recommended, so blood level testing is widely available [95].

Conclusions

GB has been an intractable cancer with short survival after diagnosis despite current standard treatment efforts. It seems polypharmacy will be

required for long-term control of GB growth until we find a core core feature of GB growth and the means to address that core feature. Perphenazine is an old, generic, and well-studied drug. Most clinicians around the world regardless of their specialty are familiar with it. This article assembled data on five areas where the biochemical and physiological attributes of perphenazine intersected with those of GB in ways that might be expected to impede GB's resistance to current treatment.

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Conflict of interests

The authors declare no conflict of interests.

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