Neuro-Oncology Practice

Repurposing existing agents as adjunct therapies for glioblastoma

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Numerous non-oncologic medications have been found in the last decade to have anti-cancer properties. While the focus in oncology research should clearly remain on deriving new therapeutic strategies, repurposing these existing medications may offer the potential to rapidly enhance the effectiveness of treatment for resistant cancers. Glioblastoma, the most common and lethal brain cancer, is highly resistant to standard therapies and would benefit from even minor improvements in treatment. Numerous agents already in the clinic for non-cancer applications have been found to also possess potential against cancer or specifically against glioblastoma. These include agents with activities affecting oxidative stress, the immune reponse, epigenetic modifiers, cancer cell metabolism, and angiogenesis and invasiveness. This review serves as a guide for potential ways to repurpose individual drugs alongside standard glioblastoma therapies.

Keywords: epigenetic, glioblastoma, immunologic, metabolic, repurposing.

Glioblastoma (GBM) is the most common and lethal primary cancer of the brain, taking 10–12 000 lives annually in the U.S. alone. Existing therapies are limited but usually provide some survival benefit. Treatment begins with maximal surgery, followed by six weeks of fractionated external beam radiotherapy and daily temozolomide (TMZ) chemotherapy. This is followed in turn by pulsed monthly dosing of TMZ until the patient demonstrates progression on MRI or clinically. Following progression, the antiangiogenic agent bevacizumab (Avastin) is often utilized alone or in combination with intravenous chemotherapy; it has shown improvement in progression-free survival and seems to show marked benefit in a subset of patients,[1] but has not yet demonstrated an improvement in overall survival in patients with GBM. Intravenous chemotherapies such as BCNU, carboplatin, and irinotecan or the oral agent CCNU are used alongside Avastin or as single agents, but generally yield benefit in only about 10%–15% of patients.[2,3] Local therapies, also with marginal benefits, include chemotherapy-loaded wafers (Gliadel) and Novocure electrical therapy. Recent studies indicate that changing TMZ dosing to a daily low-dose (metronomic) regimen salvages benefit in perhaps 10%–20% of patients, possibly through exhausting the treatment resistance enzyme MGMT or through little-studied immunologic effects.[4,5] A host of clinical trials are underway to test numerous experimental approaches to GBM—and many of these seem very promising—but there is an urgent need to enhance the current therapeutic standard-of-care. Repurposing existing drugs in an optimized fashion may be a rapid way to achieve this.

In the last one to two decades numerous medications already in clinical usage for other indications have been found to have unexpected anti-cancer mechanisms. This has led to many proposals to repurpose these medications against cancer, with benefits including immediate applicability and typically a long track record of safety in patients. It also bypasses the cost of developing a new drug, which now averages over 2.5 billion dollars. An intriguing new report from an international group has now proposed as therapy for GBM the repurposing of nine existing medications alongside metronomic temozolomide in a cocktail abbreviated as "CUSP9".[6] The nine medications all have potential anti-cancer properties, with diverse mechanisms including antiangiogenic effects, metabolic effects, and impaired cell division. The authors attempted to assess possible drug-drug interactions in the 9-drug regimen, and suggested that the 9-drug cocktail would be safe alongside the generally well-tolerated metronomic TMZ regimen.

While the CUSP9 proposal is a welcome theoretical addition to our limited repertoire against GBM, there are potential drawbacks to the regimen. With nine drugs administered at once the likelihood of side effects from one or more seems high, and given that it will be difficult to parse out the offending agent it may require stopping the entire regimen. Sequential introduction of the drugs may help somewhat with this, but synergistic or delayed toxicities will still prove problematic. Even if symptoms arise from the cancer itself or something incidental, attribution is often difficult and it will be challenging to continue the CUSP9

regimen long-term even if well-tolerated. A second issue with the proposed CUSP9 cocktail is the known lack of blood-brain barrier penetration of some of the agents. Thirdly, the repurposed drugs of CUSP9 have several divergent mechanisms, with little overlap and reinforcement of any given anticancer effect. For these and other reasons, there may be more benefit in repurposing existing drugs alongside the current state-of-the-art treatments for glioblastoma. These repurposed drugs may be able to enhance standard therapies, giving a much-needed edge against GBM. In some cases, there is already a need in the GBM patient for a given drug class—such as an anti-epileptic drug or an antihypertensive agent—and choosing ones with possible benefits against the cancer, such as valproate and losartan, may provide fringe benefits against the GBM with minimal to no drawbacks. This review summarizes numerous examples of existing drugs that may be repurposed alongside existing therapies in patients with GBM.

Functional Groupings of Drugs by Potential Anti-Cancer Activities

Group 1: Oxidative Stress

Rationale

Increasing the reactive oxygen species (ROS) within cells, boosting their oxidative stress, has been found to possibly contribute to tumorigenesis but also represents a promising metabolism-related therapeutic approach to cancer. Cancer cells typically have higher oxidative stress levels at baseline than do normal cells, but boosting the oxidative stress within cancer cells beyond a certain threshold triggers cell death.[7] Several agents have been found to do this, and increased oxidative stress appears to be an important mechanism by which standard therapies such as radiation and chemotherapy act.[7] Given the need to elevate ROS in cancer cells beyond a critical threshold, it makes particular sense to combine oxidative agents. Increased oxidative stress sensitizes to radiotherapy and chemotherapy, so the oxidative agents may be best applied alongside the initial radiation and temozolomide chemotherapy administered for newly diagnosed malignant glioma.

Disulfiram

Disulfiram (Antabuse) has been in clinical usage as an anti-alcoholism treatment for decades, but in recent years it has attracted increasing attention as a potential therapy for cancer with a good safety record and low cost. It has been specifically proposed as a therapy for GBM.[8,9] Disulfiram includes the well-established oxidative agent diamide within its structure, and disulfiram potently increases cellular oxidative stress. In addition, disulfiram appears to have other potential anti-cancer mechanisms as well. Its effects on alcohol consumption derive from its inhibition of aldehyde dehydrogenase, and this enzyme also appears to be vital in maintaining the critical GBM stem cell population.[10] Cancer stem cells have been hypothesized to give rise to all the cells within cancers, and they are resistant to standard therapies such as radiation and chemotherapy. Disulfiram may thus serve as a radiosensitizer not only by elevating ROS but also by damaging the radio-resistant subpopulation of GBM stem cells. One report also indicates a possible epigenetic mechanism for disulfiram; it was found to induce DNA demethylation in

prostate cancer.[11] It has been suggested that copper should be administered with disulfiram for maximal anti-cancer effects, but this is not yet well-established.[8] Disulfiram has modest potential for side effects, including neurologic issues, and it is of course critical that the patient be able to avoid all alcohol while taking it.

Dichloroacetate (DCA)

DCA was rarely used in children in recent decades as a therapy for certain uncommon metabolic disorders, but became the object of substantial attention on the internet following a report several years ago describing its anticancer effects.[12] A Canadian group hypothesized that through its blockade of the glycolytic enzyme PDK1, DCA would redirect cancer metabolism from glycolysis back to mitochondrial aerobic respiration, elevating ROS and potentially killing the cancer cell. This was indeed demonstrated in the Canadian team's first report, and a subsequent pilot study by the same group in five patients with GBM suggested possible clinical activity.[13] Notably, the pilot study indicated that it could take months for serum DCA concentrations to reach hypothetically effective levels, and also showed general safety albeit with some peripheral neuropathy noted. At least one clinical trial is ongoing of DCA in patients with GBM. One key caveat is that DCA is not presently FDA-approved and is not available by prescription in the U.S.; outside of a clinical trial at present, patients need to obtain it from outside sources which may be inadequate or even hazardous.

Chloroquine/Mefloquine

Chloroquine and related compounds have been in use for decades as anti-malarial medications, but in recent years have attracted interest for potential inclusion in anti-cancer regimens for their ability to inhibit autophagy.[14,15] Autophagy is a process by which cells can survive various insults and deprivations by slowing metabolism and digesting organelles and proteins not critical for short-term survival. The process typically includes digestion of mitochondria, termed mitophagy, and for this and other reasons autophagy reduces ROS. Chloroquine and related compounds have thus been shown to increase oxidative stress.[16] Chloroquine might be especially useful in combination with an agent such as DCA, which drives mitochondrial metabolism and in theory might therefore be resisted by the cancer cell with autophagy/mitophagy. While generally well-tolerated, chloroquine does not have good BBB penetration.[17] Mefloquine, another family member, has excellent BBB penetration, concentrates in the brain, and may have greater toxicity to GBM cells,[18] but it has more worrisome side effects including increased seizure risk and nightmares. It is therefore unclear which agent would be optimal for inclusion in this module, and it may depend on the individual patient's seizure risk.

Sulfasalazine

Sulfasalazine has a long track record as an agent for inflammatory bowel disease, but also inhibits the system x_c^- cystine/glutamate antiporter in the cell membrane. Inhibiting this antiporter decreases cystine availability in glioma cells, crippling a glutathione biosynthesis pathway that provides a bulwark against oxidative stress.[19]

Interestingly, another benefit of sulfasalazine for glioblastoma has been reported; by decreasing glutamate efflux from glioblastoma cells, it reduces their potential for triggering seizure activity in nearby brain.[20] It should be noted that sulfasalazine failed to demonstrate efficacy as a single agent in a clinical trial for patients with malignant glioma several years ago, but the patients had advanced, multiply-treated disease.[21]

Procarbazine

Procarbazine is an alkylating chemotherapy drug and is used relatively often in neuro-oncology as part of the PCV regimen for oligodendroglioma. However, it was also established many years ago as a potent inducer of oxidative stress.[22] One inconvenient aspect of procarbazine administration is its activity as a putative MAO inhibitor, requiring the patient to be on a tyramine-free diet while taking it. The modest MAO inhibitor activity of procarbazine also could cause a problematic interaction with disulfiram, so these agents should be combined with caution if at all.

Group 2: Immune Modulators

Rationale

Activating the immune system to better recognize glioblastoma appears increasingly promising, and based on a few isolated cases of long-term GBM survivors in vaccine trials may ultimately have curative potential. The basal immune response to glioblastoma and other cancers, as well as attempts to boost it with immunotherapy, is limited by various tumor-associated immunosuppressive mechanisms. Two of the most prominent involve the signaling pathways TGF-β and STAT3,[23,24] and this group includes agents that may be able to target both. Targeting these pathways could also have direct suppressive effects on GBM cells. This group also includes H2 blockers, which have less defined immunologic effects.[25,26] This putative immune-boosting group would likely be best alongside a current or future immunotherapy approach. It may also enhance the effects of metronomic TMZ dosing, as one report hints that continuous TMZ dosing may yield immunologic gain not conferred by standard pulsed TMZ dosing (providing an alternative explanation for the therapeutic benefit of metronomic dosing of TMZ other than exhausting MGMT).[5]

Losartan

The angiotensin II receptor inhibitors such as losartan have been found to reduce TGF-β levels systemically via an undefined mechanism. This first received major attention in a non-cancer setting, when it was shown that losartan could prevent aortic aneurysm formation in a mouse model of Marfan's syndrome.[27] In the setting of patients with GBM, a small but interesting pilot study from France recently suggested that corticosteroid requirement is reduced in GBM patients on sartans vs other antihypertensives (with the caveat that three of eighteen patients in the sartan group were on ACE inhibitors instead).[28] This may reflect the fact that TGF-β is a major driver of VEGF production;[29] reducing TGF-β with losartan might thus reduce VEGF levels. In addition to potential effects on TGF-β, GBM cells have been found to express angiotensin receptors and losartan has been found to directly affect their proliferation.[30] Losartan tends to be well-tolerated, and rarely causes hypotension even in patients lacking substantial hypertension initially. Many patients diagnosed with GBM already require an antihypertensive, providing another reason to incorporate losartan.

H2 Blocker (Cimetidine or Ranitidine)

There have long been indications that H2 blockers can modulate the immune system, though the mechanism is not well-understood. In the pediatric setting, cimetidine was long used for resistant warts in hopes it would prime the anti-papillomavirus immune response. There have also been reports of H2 blockers increasing anti-tumor immunity, particularly in the setting of colorectal cancer.[31] A large proportion of GBM patients require antacid treatment, commonly due to corticosteroid side effects—providing another rationale for use of H2 blockers. With respect to incorporating cimetidine vs ranitidine, it is unknown whether one would have a more pronounced effect on the immune system. Cimetidine may also have other actions against glioblastoma.[32] Cimetidine has a substantial impact on the p450 system, so drug interactions are more likely.

TGF-β Inhibitor

Our laboratory has evidence that a widely-used class of medications directly inhibits TGF-β signaling, and plans to publish these findings soon. A few members of this drug class demonstrate blood-brain barrier penetration, offering a more direct means than losartan to suppress TGF-β signaling.

Sunitinib (Sutent)

Sunitinib is FDA-approved for the treatment of a few cancers other than GBM, but has not been successful in trials of GBM patients.[33] It is best known as an inhibitor of VEGF, PDGF, and (to a lesser extent) FGF receptor tyrosine kinases. However, it has also been shown to inhibit STAT3,[34] though presumably not with the potency of forthcoming STAT3 inhibitors yet to reach the clinic. STAT3 has been shown to promote immune tolerance and strongly suppress the anti-tumor immune response, and this has been shown specifically in glioblastoma models as well.[35] STAT3 inhibitors are thus showing promise as boosters of cancer immunotherapy, with sunitinib the only clinically-available example of this.[36] Sunitinib's inhibition of VEGF receptor may also be helpful in terms of boosting the immune response, as VEGF signaling has been shown to play a role in immune evasion by cancer.[37] Sunitinib may therefore find unexpected utility as an enhancer of immunotherapy, despite its disappointing performance in single-agent clinical trials for glioblastoma. Sunitinib does have moderate toxicity compared to many other agents included here, such as fatigue and myelosuppression.

Group 3: Epigenetic Modifiers

Rationale

Major discoveries of the last few years have made it clear that many brain tumors are initiated and possibly driven by dysregulation of epigenetic-modifying genes. Mutation in the IDH1 and IDH2 genes, found in most Grade 2 and Grade 3 gliomas and in 5%–10% of GBM, may promote gliomagenesis through triggering hypermethylation of DNA and histones.[38] More

recently, it was found that pediatric GBM commonly harbors mutations in the histone H3.3, as well as mutations in the epigenetic modifiers ATRX and DAXX.[39] At present, two classes of epigenetic therapies have reached the clinic: histone deacetylase (HDAC) inhibitors (e.g. vorinostat/SAHA) and DNA-demethylating drugs (5-azacytidine and decitabine). It has been hypothesized that combining the two drug classes may have particular benefit against cancer, and preclinical data as well as results from a recent pilot study in lung cancer support this.[40] Inhibitors of other epigenetic regulators, such as EZH2, histone demethylases, and bromodomain proteins (e.g. the BRD4 inhibitor JQ1) are generating enthusiasm preclinically but may be years away from clinical availability.[41–43] However, existing antidepressant MAO inhibitors have been shown to inhibit the histone demethylase LSD1,[44] providing a third potential class of epigenetic modifier in this module. Furthermore, adding one of these agents to an HDAC inhibitor has been shown to yield synergistic effects against GBM cells.[45] Combining all three classes of epigenetic agents could be even more promising. This group might best be applied against IDH-mutant and pediatric GBM, given that they may be driven by aberrant epigenetic regulation.

HDAC Inhibitor (Valproate or Vorinostat)

HDACs are divided into a few classes, with class I and class II HDACs most implicated in cancer. Vorinostat (previously known as SAHA, and now marketed as Zolinza) inhibits class I and II HDACs, and is being tested in combination therapy for GBM but is FDA-approved for other cancers.[46,47] Given its significant side effects and the difficulty in obtaining it for patients with GBM, it may be preferable to use the well-established anti-epileptic drug valproate (Depakote) for its HDAC inhibitory activity. Valproate has been in wide use as an anti-epileptic drug for decades, but many years ago was shown to also act as a class II HDAC inhibitor.[48] This may explain clinical reports that glioma patients on valproate have somewhat better outcomes than those on other anti-epileptic drugs.[49–52] Interestingly, these findings have generally been stronger for pediatric vs adult glioma patients, and one could speculate this is because epigenetic lesions seem to more commonly drive pediatric glioma.

DNA-Demethylating Agent (6-Thioguanine or 5-Azacytidine or Decitabine)

The DNA-demethylating agents 5-azacytidine (Vidaza) and decitabine (Dacogen) are FDA-approved for cancers other than GBM. However, they are very difficult to obtain for patients with GBM and can have substantial side effects. As a potential alternative, the oral chemotherapy drug 6-thioguanine (6-TG) has been reported to have DNA-demethylating effects in vitro comparable to those of 5-azacytidine[53,54]—though this has not yet been confirmed specifically for GBM cells. 6-TG has previously been used for patients with glioma, is inexpensive, is typically well-tolerated, and may boost the effects of alkylating chemotherapy such as TMZ and BCNU. It may thus represent a useful substitute for the dedicated DNA-demethylating drugs 5-azacytidine and decitabine. 6-TG is typically given as a monthly pulse with doses every 6 hours for three days, but it is tempting to speculate that daily dosing might have benefits (20–60 mg daily has been found to be well-tolerated[55]).

Tranylcypromine

Tranylcypromine and phenelzine are MAO inhibitor antidepressants, now rarely used in the clinic, that have been shown to inhibit the histone demethylase LSD1 (Lysine-specific demethylase 1).[44,56] LSD1 (also called KDM1) looks to be a promising target in glioblastoma,[57] and inhibiting LSD1 may synergize with HDAC inhibition in glioma cells.[45] Tranylcypromine has been reported to be much more potent against LSD1 and is likely preferable as a putative LSD1 inhibitor.[44] One major issue with the MAO inhibitors is that their usage requires the inconvenience of a tyramine-free diet to avoid the risk of hypertensive crises.

Group 4: Metabolic Regulators

Rationale

Another approach to attacking cancer cells can be derived from suppressing their aberrant metabolism. Cancer cells rely to some degree on glycolysis as opposed to mitochondrial aerobic respiration—the so-called Warburg effect—though it has been shown that GBM cells engage in a substantial amount of both.[58] A number of drivers for aberrant cancer metabolism have been discovered, including PKM2 and HIF-1α,[59,60] and while specific inhibitors may eventually reach the clinic it is likely to take years. In the interim, there are a few available agents that show potential for interfering with cancer metabolism to some degree.

Metformin

The diabetes medication metformin is receiving increasing attention for its potential against cancer, and studies have indicated a dose-dependent decrease in cancer deaths in diabetes patients on metformin.[61] It can increase activity of AMP kinase and thus suppress activity of mTOR (more specifically the mTORC1 complex),[62] an oncogene and major driver of cell metabolism. Metformin also appears to have other effects on cancer metabolism.[63] Hyperglycemia is common in GBM patients, particularly with corticosteroid usage, often providing a more straightforward rationale for metformin usage. Metformin tends to be well-tolerated, with little induction of hypoglycemia.

mTOR Inhibitor (Rapamycin or Everolimus)

mTOR is an important oncogene and plays numerous powerful roles in GBM, notably as a driver of metabolic activity. The immunosuppressive transplant medication rapamycin is now well-established as an inhibitor of the mTOR complex mTORC1. mTOR inhibitors have generally proved disappointing to date in trials against GBM,[64,65] but some degree of this failure for rapamycin might be attributable to poor penetration into GBM masses.[66] Everolimus is another mTORC1 inhibitor specifically marketed for cancer, but rapamycin is easier to obtain for patients with GBM.

Ketogenic Diet

While not a drug, the ketogenic diet is applicable now in combination with other treatments and therefore merits inclusion. The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that has been used for decades for epilepsy. In recent years, it

has attracted interest for potential anti-cancer properties, particularly in the setting of GBM. The mechanisms of this are poorly-defined at present, but probably derive at least in part from reducing the availability of glucose as a fuel for cancer cells. This is likely to slow cancer cell metabolism, and may also trigger signaling changes such as suppressing insulin and insulin-like growth factor signaling.[67,68] The ketogenic diet may share some benefits with fasting, which recent studies suggest can directly attack cancer cells, sensitize to chemotherapy and radiation therapy, and also increase the tolerability of chemotherapy.[69,70] Disadvantages of the ketogenic diet include its complexity and inconvenience; it may be helpful for patients pursuing this to get support from a nutritionist. Some have espoused the calorie-restricted ketogenic diet for cancer patients rather than a standard ketogenic diet, but this may be challenging in patients with GBM.[71] If patients can tolerate it, there may be promise in using the ketogenic diet as a baseline with intermittent periods of fasting for 2-3 days.

Group 5: Antiangiogenic/Anti-Invasive Agents

Rationale

One hallmark of GBM is its extensive angiogenesis and vascularization. The anti-VEGFA antibody bevacizumab (Avastin) shows frequent radiographic responses in patients with GBM, but has not yet been shown to improve overall survival in unselected GBM patients.[1] One possible explanation for this is a reported increase in cancer invasiveness with VEGF inhibition,[72] which may be secondary to a boost in HIF (hypoxia-inducible factor) activity.[73] It is also possible that GBMs and other cancers can alter their profile of angiogenic factors to reduce their reliance on VEGF. There is therefore interest in combining bevacizumab with well-tolerated agents that can inhibit angiogenesis by mechanisms other than VEGF inhibition, can inhibit HIF, or can decrease invasiveness. This module may thus be most useful in combination with bevacizumab.

Captopril

Captopril is an ACE inhibitor (angiotensin-converting enzyme inhibitor) antihypertensive medication with a long safety record. It differs from other ACE inhibitors structurally in that it has a sulfhydryl group, and its purported antiangiogenic activity may stem from either ACE inhibition or from action as a sulfhydryl donor.[74,75] It should be noted that some reports demonstrate a lack of antiangiogenic activity of captopril,[76] but this activity may only be present in certain circumstances. There are cases of Kaposi's sarcoma responding to captopril alone.[77] It is well-tolerated, other than possible ACE inhibitor side effects such as hypotension, lightheadedness, and cough. One important caveat about captopril is its ability as a sulfhydryl donor to scavenge free radicals;[78] this may lead to the reduction of oxidative stress. Captopril therefore might lessen the impact of chemotherapy and radiation therapy, which as described above rely to some degree on increased oxidative stress to kill cancer cells. This should likely receive wider recognition and investigation in oncology.

Cardiac Glycosides (Digoxin and Digitoxin)

The HIF pathway is an extremely promising target in oncology. Hypoxia is common in cancer, and it triggers elevation of HIF-1α (by a mechanism involving disrupted protein degradation) and HIF-2α (by increased protein stability or up-regulated transcription) that form complexes with the constitutively-expressed HIF-1β partner.[79] These complexes drive a number of tumorigenic functions, including angiogenesis, invasion, metabolism, and cancer cell survival. At present there are no HIF inhibitors close to the clinic for patients with GBM, but it has been shown that the cardiac glycoside digoxin acts as a potent inhibitor of HIF-1α.[80] Recent reports show impressive anticancer potential of digoxin.[80,81] However, digoxin has poor blood-brain barrier penetration,[82] and the similar cardiac glycoside digitoxin may therefore be preferable. Many years ago digoxin and digitoxin were ubiquitous agents in the management of heart disease, but risk of toxicity was high and managing drug levels was tricky. Given that they are almost never used in the U.S. at this time, employing the cardiac glycosides for cancer will be challenging. However, the benefits of blocking HIF activity could make this worthwhile, given the potential for inhibiting angiogenesis, invasion, and survival of GBM cells.

Minocycline

Minocycline (or the similar doxycycline, which likely represents a comparable alternative) is sometimes used in neuro-oncology for its primary antibiotic function, in particular for the acneiform rash that can accompany erlotinib usage.[83] However, it has long been recognized to have antiangiogenic properties, possibly through inhibition of matrix metalloproteases.[84] It also appears to have other benefits, including impeding cancer cell invasiveness.[85] Minocycline and doxycycline also inhibit activity of brain microglia,[86] cells which can promote gliomagenesis and glioma invasion.

Discussion

It should be emphasized that the repurposed agents described above (and summarized in Table 1) should only be used as adjuncts to existing and forthcoming therapies. Most of the agents tend to be well-tolerated, but there are possible exceptions—such as sunitinib in the Immune modulator group and a cardiac glycoside in the Antiangiogenic/Anti-invasive group. Cumulative myelosuppression may conceivably occur with the usage of sunitinib and possibly 6-thioguanine in combination with other agents. There are few drug/drug interactions among these agents or with standard GBM therapies. In general the agents that have been included have adequate blood-brain barrier penetration, but for a few of the agents this is debatable.

Repurposing these agents alongside existing GBM therapies should be evaluated preclinically and in clinical trials alongside existing therapies, either individually or in a prescribed sequence. While these agents have multiple possible mechanisms of action, there are some rational approaches for incorporating them alongside standard therapies given the key anti-cancer mechanisms described above. The oxidative agents might best be applied with radiation and chemotherapy, and this may also be the case for the epigenetic modifiers. The immune modulators are of course likely to assist most with new immunotherapeutic approaches now in clinical trials. The antiangiogenic/anti-invasive agents might best be combined with bevacizumab, given the potential increase in invasiveness triggered by this agent.

Table 1. Summary of functional groups

Agent	Possible Mechanisms	References
Group 1—Oxidative agents		
Disulfiram	Elevates ROS; aldehyde dehydrogenase inhibitor	8–11
Dichloroacetate (DCA)	PDK1 inhibition→blocks glycolysis to increase miochondrial respiration and ROS production	12–13
Chloroquine/mefloquine	Blocks autophagy/mitophagy to increase ROS	14–18
Sulfasalazine	Inhibits system x_c- cystine/glutamate antiporter→decreases cystine for glutathione synthesis→increases ROS	19–21
Procarbazine	Oxidative agent; alkylating chemotherapy drug	22
Group 2—Immune modulators		
Losartan	Decreases TGF-β levels	27–30
Cimetidine/ranitidine	? immunomodulatory mechanism	31,32
Existing drug class blocking TGF-β—*pending*	Direct TGF-β inhibition	–
Sunitinib	STAT3 inhibition; blocks VEGFR, PDGFR, FGFR kinases	33–37
Group 3—Epigenetic modifiers		
Valproate/vorinostat	HDAC inhibition	46–52
6-thioguanine/ 5-azacytidine/ decitabine	DNA demethylation	53–55
Tranylcypromine	Inhibits LSD1 histone demethylase	44,45,56,57
Group 4—Metabolic regulators		
Metformin	Activates AMPK→inhibits mTOR	61–63
Rapamycin/everolimus	Inhibits mTOR	64–66
Ketogenic diet	Decreases glucose availability	67–71
Group 5—Antiangiogenic/Anti-invasive agents		
Captopril	Unclear antiangiogenic mechanism	74–78
Digoxin/digitoxin	HIF-1 inhibition; ? other mechanisms	79–82
Minocycline	Decreases angiogenesis and invasion by action on endothelial cells and microglia	83–86

Table 2. Other agents not included in the above functional groups that may be repurposed for treatment of GBM

Agent	Possible Mechanisms	Comments	References
Mebendazole	Antimitotic effect due to microtubule binding?	- Not available in the U.S. at this time though FDA-approved; other agents in the family are available in the U.S. - Likely BBB permeability - Single-agent clinical trials beginning	87
Itraconazole	Hedgehog pathway inhibition	Minimal BBB penetration	88
Turmeric/curcumin	NF-κB inhibition; AP-1 inhibition; Notch inhibition; other mechanisms	No viable delivery modality at present	89–91
Resveratrol	Anti-cancer mechanisms unclear	- Difficult to achieve active serum concentrations with oral delivery - Unknown BBB penetration	92,93
Valganciclovir/ Valcyte	Anti-CMV activity	CMV may contribute to gliomagenesis and possibly also to glioma maintenance	94,95
Marijuana/THC	Unknown mechanism for anti-glioma effects	- Difficulties in accessing marijuana - Marinol/THC can be prescribed, but lacks possible benefit from cannabinoids other than THC	96
Aprepitant	Blocks NK1 receptor	NK1 receptor promotes GBM cell proliferation	97
Tetrathiomolybdate	Copper chelation	Copper chelation can decrease angiogenesis	98
Tamoxifen	Unclear mechanism; may act on GBM cells via nonclassical estrogen receptors	Has been utilized for many years, often as a single agent, for patients with GBM when other options are not available	99

There are rationales for other combinations as well. While the antiangiogenic/anti-invasive agents could work well in combination with bevacizumab, the immune-modulating agents would also be reasonable in combination with bevacizumab given the immunosuppressive effects of its target VEGF-A. It is also worth considering application of these agents for glioblastomas with certain genetic features. For example, the epigenetic-modifying agents module could have greater potential vs pediatric or IDH-mutant glioblastomas, given that aberrant epigenetic regulation may drive these cancers.

There are a number of other medications that could be repurposed for GBM and other cancers that did not fit into these functional groups but may be useful. These are summarized in Table 2, and there are doubtless some that have been missed here.

It is important to underscore the limitations of this work. While testing these agents in clinical trials is important, such trials would likely be complex, expensive, and difficult to perform. In addition, some of the agents included in these modules have multiple mechanisms of action and diverse effects, enabling their inclusion in more than one of these functional groups. From a practical perspective, it should be noted that a few of the agents included above are very expensive anti-cancer agents not FDA-approved at this time for patients with GBM. This includes vorinostat, azacytidine/decitabine, everolimus, and sunitinib. Insurance companies are unlikely to approve coverage of these agents, presenting an often insurmountable obstacle in the clinic. However, in most cases above there are inexpensive alternatives proposed.

While there is a clear need for further evaluation of these agents alongside standard GBM therapies, it is possible to apply some of them now in a limited fashion. Given the very limited armamentarium for patients with GBM and the safety and availability of the repurposed agents, a case could be made to utilize these agents now for patients without good options. Additionally, though this review focuses on GBM, repurposing these agents may have utility for other cancers as well.

Funding

Acknowledgments

Conflicts of interest statement. None declared.

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