

Repurposing some older drugs that cross the blood–brain barrier and have potential anticancer activity to provide new treatment options for glioblastoma

Dayle Rundle-Thiele,¹ Richard Head,² Leah Cosgrove³ & Jennifer H. Martin⁴

¹School of Medicine, Flinders University, Bedford Park, SA, Australia, ²Future Industries Institute, Research and Innovation Portfolio, University of South Australia, Adelaide, SA, Australia, ³CSIRO, Human and Nutrition Flagship, Adelaide, SA, Australia and ⁴School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia

Correspondence

Ms Dayle Rundle-Thiele, c/o Course Administration Unit, School of Medicine, Flinders University, Room 5E209 Level 5, Flinders Medical Centre, Bedford Park, SA, 5042, Australia.

Tel.: +61 (4) 2295 7632

Fax: +61 (8) 8204 5675

E-mail: rund0028@uni.flinders.edu.au

Keywords

antidepressants, antiepileptic drugs, antihypertensive, beta-blockers, glioblastoma, statins

Received

31 March 2015

Accepted

10 September 2015

Accepted Article Published Online

16 September 2015

Glioblastoma is a brain neoplasm with limited 5-year survival rates. Developments of new treatment regimens that improve patient survival in patients with glioblastoma are needed. It is likely that a number of existing drugs used in other conditions have potential anticancer effects that offer significant survival benefit to glioblastoma patients. Identification of such drugs could provide a novel treatment paradigm.

Glioblastoma: current knowledge of therapeutics

Glioblastoma (GBM) is the most common and most lethal form of primary brain tumour worldwide [1]. Most often, GBM is diagnosed at between 45 and 70 years of age [2]. Currently, the standard treatment for patients with GBM involves tumour resection followed by radiotherapy and administration of a chemotherapeutic agent, temozolomide (TMZ). In spite of current treatment regimens, survival remains poor; median survival time ranges from 12 to 16 months [2, 3]. To date, no additional treatment strategies that prolong overall survival (OS) further have been identified [4]. Developments of new treatment regimens that improve patient survival in patients with GBM are needed. It is likely that a number of existing drugs used to treat other conditions have potential anticancer effects that offer significant survival benefit to GBM patients.

Identification of such drugs could provide a novel treatment paradigm.

One significant limitation to the standard treatment protocol is tumour cell resistance to TMZ. O⁶-methylguanine methyltransferase (MGMT) is a DNA repair protein which confers cellular resistance to TMZ [5]. Spontaneous methylation, and subsequent silencing, of the *MGMT* gene promoter occurs in up to 50% of patients with GBM and has been associated with a significant increase in OS compared to patients with unmethylated *MGMT* promoters [6]. For patients with unmethylated *MGMT* gene promoters, who may not respond well to standard treatment, there are currently no alternative treatment options. Furthermore, given that survival in all patients remains poor, more effective regimens are required.

In order to consider pharmacological agents that might have potential in the treatment of GBM, a thorough knowledge of GBM cancer biology is required. In summary, it is

well documented that the growth and pathogenesis of GBM is driven by various genetic and epigenetic aberrations [7–10]. A number of recent studies have reported on the heterogeneous nature of GBM [4, 8, 10]. Given this, it is probable that within a single tumour there are subpopulations of cells with different genetic alterations and potentially different susceptibilities to chemotherapeutic agents [11]. It is unlikely that a ‘single-hit’ treatment strategy will provide significant benefit to many patients diagnosed with GBM. The administration of several therapeutic agents will allow clinicians to target a range of GBM phenotypes and, as such, therapy involving multiple adjuvants might provide more benefit than standard chemotherapy with TMZ alone.

Two of the main pathological features of GBM include increased cellular proliferation and angiogenesis (Figure 1) [8]. Increased cellular proliferation is a hallmark of neoplasia and in the context of GBM probably results from aberrant growth factor signalling, inactivation of tumour suppressor pathways (such as the p53 and retinoblastoma pathways), upregulation of the phosphatidylinositol 3-kinase (PI3K) pathway [8] and epidermal growth factor receptor (*EGFR*) gene mutations [10]. In GBM, extensive angiogenesis might be attributed to elevated levels of vascular endothelial growth factor (VEGF) and might also involve fibroblast growth factor (FGF), nerve growth factor (NGF) and angiotensin II [12, 13].

Additional pathological features of GBM include changes to the stromal environment such as necrosis, hypoxia and peritumoural oedema (Figure 1) [9, 14]. A number of studies have reported that hypoxia might stimulate angiogenesis and increase vascularity through the upregulation of hypoxia-inducible factor 1 (HIF-1) [15, 16]. Furthermore, hypoxic tumour cells are known to be resistant to radiotherapy, and this might also be attributed to

the upregulation of HIF-1 [17–19]. There is evidence in the literature that hypoxia might also confer tumour cell resistance to chemotherapy [20, 21]. Several studies have shown that peritumoural oedema and necrosis in GBM have been associated with poor patient survival [9, 14].

At present, there is a pressing need to explore alternate treatment options which could improve OS and quality of life in patients with GBM. Given this, the principal aim of the present review was to identify existing drugs or therapeutic agents already registered or used in previous clinical trials that might impair one or more of the pathological processes of gliomagenesis outlined above (these will be referred to as antineoplastic drugs or antineoplastic agents), and therefore be helpful to consider in a clinical trial development portfolio.

Method

A literature search was conducted using the PubMed database. MeSH search terms and subheadings included glioma; GBM; brain neoplasms, treatment; therapeutics, combined drug therapy; therapeutics, blood–brain barrier; and pharmacology, therapeutic use. The search was restricted to primary research articles published in English. Studies were selected for review based on the inclusion of a drug that crosses the blood–brain barrier (BBB), that is primarily prescribed for noncancer indications and that might have antineoplastic actions. The ability of a drug or its active metabolite to cross the BBB and reach the tumour is paramount in the treatment of brain neoplasms. For the purpose of the present review, the ability of a drug to cross the BBB was determined using clinical pharmacology and therapeutics principles and clinical experience; drugs known to act

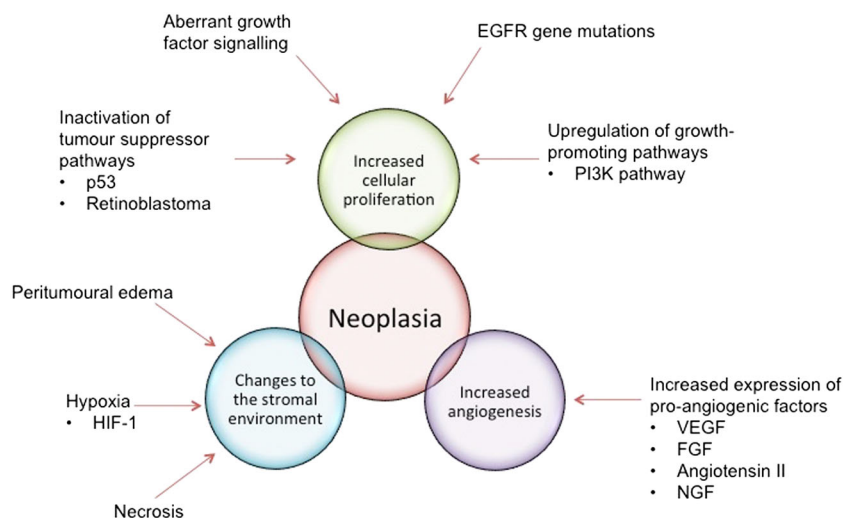


Figure 1

The main pathological features of glioblastoma. EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; HIF-1, hypoxia-inducible factor 1; PI3K, phosphatidylinositol-3 kinase; NGF, nerve growth factor; VEGF, vascular endothelial growth factor

in the central nervous system (CNS) or to elicit side effects in the CNS were included.

Exploration of the existing literature revealed a number of drug classes that might improve survival in patients with GBM. We restricted the present review to include drugs that are currently marketed, widely used in clinical practice and with favourable side-effect profiles. This is because there is a short time to clinical use, and there is little point in developing drugs that cannot be used because of a life-threatening side-effect profile. In particular, we focused the present review on several agents within the following categories, with the belief that these are the most promising targets for future research: histone deacetylase inhibitors (HDACi), drugs that inhibit neurotransmitters, beta-adrenoceptor antagonists (beta-blockers), statins and antihypertensive medications. A total of 45 studies were included in the present review. It is important to note that this was not a comprehensive review of all drugs that might be useful in the treatment of GBM. Additional drug classes that might improve patient survival include antimalarial drugs, antiviral drugs, drugs used in the treatment of diabetes and anti-inflammatory medications; however, these were not included in the present review. These additional drug classes are reviewed briefly in the conclusions.

Drugs that inhibit neurotransmitters

Psychotropic agents are well known to influence neurotransmission and have more recently been shown to have antiproliferative effects that might be valuable in the treatment of neoplasms [22, 23]. Several subclasses of psychotropic drugs, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), phenothiazines and antiepileptic drugs (AEDs; these will be reviewed later), have been investigated as potential adjuvants for cancer therapy [7, 22–24]. The TCAs act at presynaptic adrenoceptors and serotonin receptors in the CNS to block the reuptake of noradrenaline and serotonin, respectively. SSRIs are more specific and act only on presynaptic serotonin receptors to prevent serotonin reuptake. Phenothiazines are dopamine receptor antagonists traditionally indicated for use in the treatment of psychosis and chemotherapy-induced emesis.

Recently, TCAs (amitriptyline, imipramine, clomipramine, doxepin and citalopram) and SSRIs (paroxetine, fluoxetine and sertraline) have been reported to reduce tumour cell proliferation in a number of cell lines, including rat C6 glioma, human neuroblastoma and human astrocytoma cell lines [22, 24–26]. Reduced cellular proliferation might occur through several mechanisms. Two recent studies showed an increase in caspase-3 activity (a cysteine protease involved in the induction of the apoptotic cascade) in response to treatment with TCAs and SSRIs [22, 25]. Contrary to this hypothesis, Tzadok *et al.* [26] demonstrated

decreased cell proliferation in response to antidepressant treatment, with an absence of increased caspase-3 activity, and hypothesized the involvement of the mitogen-activated protein kinase pathway. A recent *in vivo* study by Walker *et al.* [24] investigated TCA use and mortality in patients with glioma or colorectal cancer. In a sample of 2592 patients with glioma and 22 524 patients with colorectal cancer, 4.1–4.2% of patients reported the use of low-dose TCAs for the period of at least two prescriptions; however, there was no significant reduction in mortality associated with the use of TCAs in patients with glioma or colorectal cancer.

Several studies have reported on the potential anti-neoplastic activity of dopamine receptor antagonists, including chlorpromazine, thioridazine and perphenazine [23, 26, 27]. Tzadok *et al.* [26] found a significant additive antiproliferative effect following treatment of U87 glioma cells with TMZ and perphenazine. Perphenazine crosses the BBB and has a strong predilection for the blockage of D2 and D3 dopamine receptors. These receptors have been implicated in gliomagenesis through stimulation of neuronal stem cells within the subventricular zone (SVZ) in the lateral ventricles [28]. Blockade of D2 and D3 receptors in the SVZ might improve survival in GBM [28]. Yde *et al.* [27] reported increased sensitivity of breast cancer cells to a first-line therapeutic agent, tamoxifen, with adjuvant chlorpromazine therapy. Furthermore, Sachlos *et al.* [23] demonstrated that treatment with thioridazine reduced proliferation in acute myeloid leukaemia cell lines, potentially through selective targeting of cancer stem cells. To the best of our knowledge, there is no existing research regarding the efficacy of chlorpromazine and thioridazine as adjuvant anticancer agents in GBM.

AEDs

Epileptic seizures are a common complication of GBM, occurring in 22–60% of patients, and often treatment with an AED such as valproate (VPA), phenytoin, carbamazepine or levetiracetam (LEV) is required to provide symptomatic relief [29]. A large number of studies have found a potential benefit of HDACi such as VPA in the treatment of GBM [30–32]. Furthermore, other AEDs have also been hypothesized to offer a survival benefit in patients with glioma [33–35]. HDACi and other AEDs are reviewed below.

HDACi

VPA has a wide spectrum of antiseizure activity and has recently been suggested as a potential adjuvant in cancer treatment [36]. It is known to act on gamma-butyric acid (GABA) levels in the brain, to block voltage-gated sodium, potassium and calcium channels and to inhibit histone deacetylases [36]. Abnormal activation of histone

deacetylases can induce neoplasia; deacetylation of histones promotes the condensation of chromatin and repression of the transcription of several genes. HDACi can trigger hyperacetylation of histones, promoting growth arrest and apoptosis [31, 35, 37]. Furthermore, inhibition of chromatin condensation might increase the availability of target DNA to alkylating chemotherapeutic agents, and enhance therapy [32, 38].

A number of recent studies have reported the anti-neoplastic effects of VPA using human glioma cell lines [31, 32, 38]. Adjunctive treatment of glioma cell lines with VPA provided an additive effect on inhibition of cellular proliferation following treatment with TMZ. Furthermore, treatment with VPA has been shown to increase tumour cell sensitivity to radiotherapy [31, 32, 38]. The mechanisms by which VPA might enhance the cytotoxic effects of TMZ and radiation are unknown. In addition, it has been reported that VPA might increase cellular levels of the MGMT protein [30, 38]. In spite of this, VPA is still widely acknowledged to have an antiproliferative effect in glioma cells.

In addition to VPA, some of the newer AEDs, including topiramate (TPM) and the major active metabolite of LEV, 2-pyrrolidinone-n-butyric acid (PBA), might act as HDACi [37]. LEV is a newer AED, traditionally indicated for use as monotherapy in the treatment of partial focal seizures. Bobustuc *et al.* [30] found that treatment with LEV + TMZ significantly reduced cellular proliferation in several GBM cell lines. Furthermore, LEV was reported to have an inhibitory effect on MGMT protein expression in GBM cell lines but not in normal human astrocyte cells. It was hypothesized that increased levels of the p53 protein in cells treated with LEV enhanced p53 binding and inhibition of the *MGMT* gene promoter, consequently downregulating expression of the MGMT protein and enhancing tumour cell sensitivity to TMZ [30].

TPM is a newer AED, with several mechanisms of action that might contribute to antiseizure effects [39]. TPM, in addition to VPA, is classified as a category D drug in pregnancy, owing to an increased risk of fetal malformation [40, 41]. Two studies have demonstrated potential antimetastatic and antiangiogenic effects of TPM in mice injected with Lewis lung carcinoma [42, 43]. In the earlier study, Ma *et al.* [42] demonstrated that treatment with TPM for 20 days strongly inhibited tumour metastasis in a dose-dependent manner. More recently, these authors [43] reported that treatment with TPM for 21 days resulted in a significant reduction of VEGF expression, suggesting that TPM might effectively decrease tumour angiogenesis. It is unknown whether TPM would have similar effects in glioma cells.

Other AEDs

Enzyme-inducing AEDs (EIAEDs), including carbamazepine and phenytoin, potentially induce components of

the cytochrome P450 system in the liver and consequently enhance the metabolism of chemotherapeutic agents and other drugs, including steroids that are metabolized by the same system. As such, concomitant treatment with EIAEDs might increase the dosage requirements of chemotherapeutic agents and have an effect on patient outcomes [33–35], and this is an important consideration in GBM pharmacotherapy.

Several studies have reported on the use of EIAEDs and non-EIAEDs in patients with GBM [7, 33, 34]. Jaeckle *et al.* [33] investigated the use of AEDs in 620 patients with GBM; 432 patients received treatment with an EIAED, 14 were prescribed a non-EIAED and 159 did not receive any AED. The median OS in the patients who were prescribed an EIAED was 12.3 months compared to 10.7 months for patients in the other two groups. By contrast, a previous study by Oberndorfer *et al.* [34] found that, within a retrospective cohort of 168 patients with GBM (of whom 37 were prescribed a non-EIAED and 43 were prescribed an EIAED), OS was 13.7 months for patients who were prescribed a non-EIAED compared to 10.8 months in patients prescribed an EIAED. More recently, a study by Weller *et al.* [35] reported on the use of AEDs in a retrospective cohort of 573 patients with GBM, of whom 110 patients were treated with a non-EIAED (predominantly VPA) and 277 patients received treatment with an EIAED. These authors found a significant survival benefit for patients treated with VPA compared to those taking other AEDs (including EIAEDs) or no AED [35]. A similar retrospective study of 544 patients with primary GBM by Barker *et al.* [7] reported on the use of AEDs (including phenytoin, LEV, carbamazepine, phenobarbital and VPA) in 403 patients. The median OS of patients in the study was 14 months, irrespective of treatment modality. The median OS in patients treated with VPA was 16.9 months, and in those treated with radiation therapy + TMZ + VPA was 23.9 months, compared to 15.9 months without VPA. However, only a small number ($n = 29$) of patients were treated with VPA. Recently, there has been a large focus on VPA as a first-line AED in the treatment of GBM.

Statins

Statins are traditionally prescribed to treat hypercholesterolaemia. More recently, statins have been indicated as potential adjunctive treatments in several cancers, owing to inhibitory effects on cellular signalling pathways involved in proliferation, migration, invasion and induction of apoptosis [44–47]. The primary mechanism by which statins act is inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, preventing the conversion of HMG-CoA to mevalonate [48]. Important downstream products of mevalonate include cholesterol, Ras, Raf and Rho [48, 49]. Gabrys *et al.* [48] discovered

that growth in glioma cells might be highly dependent on the mevalonate pathway. As such, this pathway is a significant target for potential antineoplastic therapies.

Several recent *in vitro* studies have found statins to have proapoptotic and cytotoxic effects on glioma and other cancer cells [50, 51]. Tapia-Perez *et al.* [50] demonstrated statin-mediated toxicity in human glioma cell lines U87, U138 and LN405, and in one rat glioma cell line, RGI1, treated with simvastatin and lovastatin. This observed cytotoxicity was likely to have been due to stimulation of the proapoptotic protein, Bim. By contrast, Wood *et al.* [51] found an increase in levels of Bcl 2 (an antiapoptotic protein) in rats exposed to chronic administration of simvastatin (50 mg kg⁻¹ day⁻¹ for 21 days). In humans, the highest daily dose of simvastatin would equate to approximately 0.07 mg kg⁻¹ day⁻¹, much lower than the dosage used in the study by Wood *et al.* [51].

Additional *in vitro* studies have reported on the antiproliferative effects of statins on several cancer cell lines [46, 48, 49]. Yanae *et al.* [46] investigated the treatment of rat C6 glioma cells and human-derived U251MG GBM cells with mevastatin, fluvastatin and simvastatin. In this study, 5 µM of mevastatin and simvastatin, and 2.5 µM of fluvastatin inhibited cell proliferation and induced apoptosis in both cell lines. Yanae *et al.* [46] stated that the peak plasma concentration of fluvastatin in humans is less than 2 µM. Similarly, Wu *et al.* [49] found a 35% reduction in cellular proliferation in U87 and U251 human GBM cells treated with simvastatin compared to control cells. Gabrys *et al.* [48] demonstrated that lovastatin (0.625–50 µM) inhibited proliferation in U87MG and FaDu (hypopharyngeal squamous cell carcinoma) cell lines in a dose-dependent manner. Mechanisms contributing to the inhibitory effects of statins on cellular proliferation might include inhibition of cell cycle progression as a result of decreased cellular signalling [48, 49]. Furthermore, a study by Yongjun *et al.* [47] reported decreased cell migration in a U87 glioma cell line in response to treatment with atorvastatin, probably due to inhibition of matrix metalloproteinase (MMP) 2).

Antihypertensive drugs

Antihypertensive agents include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists/blockers (ARBs) and beta-blockers (these will be reviewed later) and are typically prescribed to treat hypertension, congestive heart failure and diabetic nephropathy. ACEIs reduce the production of angiotensin II, whereas ARBs selectively inhibit the activation of the angiotensin II type 1 receptor [52]. Angiotensin II plays an important role in the regulation of fluid and electrolyte balance and is also involved in cell growth,

differentiation, apoptosis and angiogenesis [53, 54]. Existing research has hypothesized an antineoplastic role for ACEIs and ARBs, primarily due to the inhibition of angiotensin II [53, 55].

Rivera *et al.* [55] investigated the effects of treatment with an ARB, losartan, in 12-week-old rats implanted with rat C6 glioma cells and found a significant decrease in cell proliferation and a decrease in the number of capillary vessels in tumours resected from rats treated with either 40 mg kg⁻¹ or 80 mg kg⁻¹ once daily compared to controls. A more recent study from the same group reported a significant decrease in tumour volume following 30 days of treatment with either 40 mg kg⁻¹ or 80 mg kg⁻¹ losartan once daily compared to controls [53]. Furthermore, Arrieta *et al.* [53] showed increased apoptosis and decreased levels of the proangiogenic factors VEGF, platelet-derived growth factor and FGF in rat C6 glioma cell lines treated with losartan compared to controls. A study by Rooprai *et al.* [56] demonstrated downregulation of MMP-2 and MMP-9 in four cell lines (an ependymoma, an oligoastrocytoma, an anaplastic astrocytoma and a GBM cell line) in response to treatment with the ACEi captopril. MMPs are thought to play a role in the degradation and remodelling of the extracellular matrix and might be critically involved in GBM metastasis and invasion; as such, captopril might have potential anti-invasive effects [57].

A number of retrospective analyses have investigated the impact of antihypertensive treatment on patient outcome in several cancers [12, 52, 58–60]. Cardwell *et al.* [58] reported on the use of ACEIs and/or ARBs after diagnosis with either breast, colorectal or prostate cancer in over 20 000 patients in the UK. This study found a small, nonsignificant reduction in cancer-specific mortality in colorectal and prostate cancer patients treated with an ACEi. Overall, there was no significant impact on all-cause mortality for patients treated with either an ACEi or ARB. Holmes *et al.* [59] found that treatment with ACEIs, ARBs and/or beta-blockers had no significant survival benefit in a sample of over 3000 Canadian patients with either breast, colorectal, lung or prostate cancer. Chae *et al.* [12] investigated the use of antihypertensive agents in 1449 patients with breast cancer. This study found no significant decrease in OS for patients prescribed antihypertensive medications, although treatment with ARBs was associated with a decreased risk of recurrence compared to controls. A smaller study by Engineer *et al.* [52] showed that combination treatment with a beta-blocker and either an ACEi or ARB decreased progression and decreased hospitalizations over a 4-year period in a sample of 262 patients with colorectal cancer compared to patients taking either a beta-blocker or an ACEi/ARB. One study investigating the effect of treatment with ACEIs/ARBs in GBM demonstrated no significant survival benefit [60]. Interestingly, Carpentier *et al.* [60] reported a significant reduction in preoperative

oedema (as visualized on magnetic resonance imaging) in patients treated with either an ARB/ACEI compared to controls, probably due to a reduction in neovascularization that normally enables the development of extensive peritumoural oedema. Furthermore, treatment with an ACEI/ARB resulted in a significant reduction in steroid treatment requirements.

Doxazosin is an α -1 adrenoceptor antagonist that has been used to treat hypertension and benign prostatic hyperplasia. A recent study by Petty *et al.* [61] found that doxazosin inhibited the migration of A172 glioma cells in a dose-dependent manner. In the same study, mice were implanted with prostate cancer cells and subjected to either treatment with doxazosin for 10 days or to a control treatment. The authors demonstrated a significant reduction in the number and size of lung metastases in treated mice compared to controls. They hypothesized that doxazosin might cause activation of the erythropoietin-producing hepatocellular A2 family of receptor tyrosine kinases involved in the induction of apoptosis, and inhibition of proliferation and migration.

Beta-blockers

Beta-blockers are commonly prescribed in the treatment of hypertension and in prevention of cardiovascular diseases [62, 63]. Studies have suggested that these agents might inhibit angiogenesis, invasion and cellular proliferation, as well as increasing apoptosis in several cancer cell lines [64–66]. The most extensively studied beta-blocker in relation to potential utility as an adjunctive treatment in neoplasia is propranolol, a nonselective beta-blocker that competes with adrenaline and noradrenaline binding at beta-1- and -2 adrenoceptor sites [62, 63]. Evidence in the existing literature suggests that blockade of adrenergic stimulation by beta-blockers might decrease the expression of proangiogenic factors, including VEGF, MMP-2 and MMP-9; however, the mechanism by which this occurs is largely unknown [62, 67, 68]. Chim *et al.* [16] hypothesized that decreased levels of hypoxia-inducible factor 1 associated with propranolol treatment caused a decrease in VEGF levels in haemangioma endothelial cells.

Pasquier *et al.* [64] investigated the use of propranolol in several cell lines, including human breast cancer, neuroblastoma and U87 GBM cell lines. In this study, treatment with propranolol resulted in decreased proliferation in all cell lines compared to controls. Results were not reported for antiangiogenic effects of propranolol in the U87 GBM cell line. A subsequent study by Pasquier *et al.* [65] examined the effect of a number of beta-blockers, including metoprolol, carvedilol, nebivolol, propranolol, butoxamine and atenolol, on two neuroblastoma cell lines. The mixed alpha/beta-receptor antagonist, carvedilol; the selective beta-1 adrenoceptor

antagonist, nebivolol; and propranolol were reported to have significant antineoplastic effects involving the induction of apoptosis and increased cell cycle arrest compared to controls. Currently, there is little evidence in the literature to support the use of selective or mixed beta-blockers over propranolol as an adjunct in cancer treatment.

The mechanism by which beta-adrenoceptor antagonists might promote apoptosis is not yet understood. Kozanoglu *et al.* [67] reported that treatment with propranolol resulted in increased expression of the proapoptotic gene *Bcl-10*, decreased expression of the antiapoptotic gene *Bcl-2* and decreased activation of the nuclear factor-kappa B (NF-kappa B) pathway in human U266 multiple myeloma cells. NF-kappa B is a transcription factor critically involved in many cellular processes, and excessive activation of the NF-kappa B pathway has been linked to the promotion of cellular proliferation and inhibition of apoptosis [69].

Conclusions

GBM is a relatively rare cancer, with an incidence of 2–4 per 100 000 adults per year worldwide that is unlikely to receive significant research funding or support. Given that drug development is associated with considerable time and financial costs to the pharmaceutical industry, research teams, governments and patients, alternative strategies are required to develop more efficient and timely therapeutic protocols. The ability to use currently marketed drugs in the treatment of GBM provides a financially practicable approach to encourage the development of new therapeutic regimens to improve OS in patients with GBM.

We have demonstrated in the present review that a number of drugs currently in routine use, including antidepressants, AEDs, statins, beta-blockers and other anti-hypertensive agents, exhibit promising antineoplastic effects *in vitro*. We believe that these drug classes offer the most promising survival benefit in GBM. Many of the drugs presented here have been shown to antagonize one or more of the pathological features of GBM. Furthermore, a number of drugs, including VPA, may potentiate the effects of standard radiotherapy and chemotherapy treatments. It is important to note that the drugs presented here do not comprise an exhaustive list of potential therapeutic agents for patients with GBM. Table 1 presents a summary of the indication for use, mechanism of action and potential antineoplastic effects of the afore-mentioned drugs.

Recent research has identified additional classes of drugs that might have survival benefit in GBM. These drug classes have been excluded from the present review owing to poor side-effect profiles and/or limited available data. Nonsteroidal anti-inflammatory drugs – in particular, celecoxib – have been investigated as adjuvants in glioma therapy owing to their ability to enhance radiosensitivity in glioma cell lines; however, celecoxib was recently shown

Table 1

 Existing drugs with potential antineoplastic effects as demonstrated through *in vitro* studies.

Class Drug	Primary indications for use	Primary mechanism of action	Mechanism of antineoplastic effects	References
Tricyclic antidepressants Amitriptyline Imipramine Clomipramine Doxepin Citalopram	Major depression Neuropathic pain Migraine prophylaxis	Inhibit reuptake of noradrenaline and serotonin at presynaptic nerve terminals	Reduce cellular proliferation and might induce apoptosis through aberrant MAPK pathway activity or inhibition of mitochondrial activity	Levkovitz <i>et al.</i> [22], Higgins and Pilkington [25], Tzadok <i>et al.</i> [26]
Selective serotonin reuptake inhibitors Paroxetine Fluoxetine Sertraline	Major depression Bipolar disorder Anxiety disorders Bulimia nervosa	Inhibit reuptake of serotonin at presynaptic nerve terminals	Reduce cellular proliferation and might induce apoptosis through aberrant MAPK pathway activity or inhibition of mitochondrial activity	Levkovitz <i>et al.</i> [22], Higgins and Pilkington [25], Tzadok <i>et al.</i> [26]
Phenothiazines Chlorpromazine Thioridazine Perphenazine	Chemotherapy-induced emesis	Dopamine receptor antagonists	Might decrease cellular proliferation and increase cellular sensitivity to some chemotherapeutic agents	Sachlos <i>et al.</i> [23], Tzadok <i>et al.</i> [26], Yde <i>et al.</i> [27]
Valproic acid (valproate)	Seizure disorders Bipolar disorder Migraine prophylaxis	Acts on GABA levels in the brain to reduce voltage-gated sodium, potassium and calcium channels	Acts as a histone deacetylase inhibitor and might contribute to chromatin condensation, growth arrest and apoptosis	Camphausen <i>et al.</i> [31], Chinnaiyan <i>et al.</i> [32], van Niffterik <i>et al.</i> [38]
Levetiracetam	Partial focal seizures Adjunct in tonic-clonic and myoclonic seizures	Unknown	Might act as a histone deacetylase inhibitor, contributing to chromatin condensation, growth arrest and apoptosis	Bobustuc <i>et al.</i> [30]
Statins Lovastatin Pravastatin Rosuvastatin Simvastatin	Hypercholesterolaemia Prevention of cardiovascular disease Glaucoma	Inhibition of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol synthesis pathway	Decreased activity in cell signalling pathways contributes to induction of apoptosis and decreased proliferation	Yanae <i>et al.</i> [46], Yongjun <i>et al.</i> [47], Gabrys <i>et al.</i> [48], Wu <i>et al.</i> [49], Tapia-Perez <i>et al.</i> [50]
Angiotensin-converting enzyme inhibitors Captopril	Hypertension Diabetic nephropathy	Decrease production of angiotensin II by inhibition of angiotensin converting-enzyme	Decreased proliferation and angiogenesis. Might also decrease invasion and migration via reduction of MMP-2 and MMP-9 expression	Rooprai <i>et al.</i> [56]
Angiotensin receptor blockers Losartan	Hypertension Diabetic nephropathy	Antagonists at angiotensin II type 1 receptors	Decreased angiogenesis as a result of decreased VEGF expression	Arrieta <i>et al.</i> [53], Rivera <i>et al.</i> [55]
Other antihypertensives Doxazosin	Hypertension Benign prostatic hyperplasia	Antagonist at alpha-1 adrenoceptors	Reduction of cell migration, proliferation and apoptosis through activation of Ephrin A2 receptors	Petty <i>et al.</i> [61]
Beta-blockers Propranolol* Butoxamine Metoprolol Nebivolol	Hypertension Prevention of cardiovascular disease	Antagonists at beta-1 and/or beta-2 adrenoceptors	Reduction of angiogenesis through decreased expression of VEGF and MMP-9. Also decreases cell proliferation through unknown mechanisms	Kozanoglu <i>et al.</i> [67], Pasquier <i>et al.</i> [64]

GABA, gamma-aminobutyric acid; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor. *The majority of studies reporting on anti-neoplastic effects of beta-blockers involved only propranolol.

to have no survival benefit in combination with TMZ and thalidomide in a Phase II study [70, 71]. Drugs used in the treatment of diabetes, including metformin and pioglitazone, might inhibit glioma cell growth [72, 73]. A number of studies have reported that the antimalarial drug,

chloroquine, may enhance the cytotoxic effects of TMZ in glioma cell lines [74, 75]. Disulfiram, a drug used in the maintenance of alcohol abstinence, has been demonstrated to reverse tumour cell resistance to TMZ [76]. Antiviral therapy with acyclovir and valganciclovir has also been

hypothesized to offer a survival benefit in GBM [77, 78]. Furthermore, it is likely that a number of older drugs that have been withdrawn from use might also exhibit antineoplastic effects, especially in combination with radiotherapy.

As evident in the current literature, the majority of studies reporting on the possible antineoplastic effects of existing therapeutic agents are limited to *in vitro* investigations, in cell lines with known differences and a lack of heterogeneity in gene expression and activity against human cancers. Further, the concentration of drug used during *in vitro* experiments often exceeds by several-fold the *in vivo* concentration achieved with the therapeutic dosage of a given drug. It is uncertain whether antineoplastic effects reported from *in vitro* studies would be observed during *in vivo* trials. The majority of human studies to date have been limited to retrospective analyses. In these cases, researchers are unable to investigate the effects of different dosages of drugs or different phenotypic variables, and research is limited when only a small number of patients are prescribed any given drug.

There have been few studies reporting on the concurrent use of more than one class of drug for the treatment of GBM and cancer cell lines. Multidrug therapy introduces many challenges, including the management of drug interactions and the cumulative risk of additional adverse effects. In the case of GBM, where survival remains extremely poor, it is likely that the therapeutic benefits of multidrug adjunctive therapy and the known safety profile of these older drugs would greatly outweigh any therapeutic risk.

Currently, new therapeutic regimens are required to improve OS in patients with GBM. Given the evidence presented in the present review, future randomized controlled trials incorporating existing agents with potential antineoplastic effects into current therapy could demonstrate an enhancement of the treatment protocol. However, in spite of their limitations, preliminary *in vitro* and retrospective *in vivo* studies to determine effective and appropriate dosing, as well as effective drug combinations, are required. Furthermore, a retrospective *in vivo* study of patients with GBM, correlating OS and progression-free survival with individual patients' prescription medication, should be carried out to provide more information on the potential survival benefit obtained from adjunctive treatment with existing drugs.

Conflict of Interest/Disclosure

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted

work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Contributors

DR-T wrote the manuscript. JHM was involved in the design of the research, the development of ideas and the preparation of the manuscript. LC was involved in the development of ideas and acted as a scientific adviser. RH was involved in the design of the research, the development of ideas and the preparation of the manuscript, and acted as a scientific adviser.

REFERENCES

- 1 Reardon DA, Wen PY. Therapeutic advances in the treatment of glioblastoma: rationale and potential role of targeted agents. *Oncologist* 2006; 11: 152–64.
- 2 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987–96.
- 3 Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009; 10: 459–66.
- 4 Kast RE, Boockvar JA, Bruning A, Cappello F, Chang WW, Cvek B, Dou QP, Duenas-Gonzalez A, Efferth T, Focosi D, Ghaffari SH, Karpel-Massler G, Ketola K, Khoshnevisan A, Keizman D, Magne N, Marosi C, McDonald K, Munoz M, Paranjpe A, Pourgholami MH, Sardi I, Sella A, Srivenugopal KS, Tuccori M, Wang W, Wirtz CR, Halatsch ME. A conceptually new treatment approach for relapsed glioblastoma: coordinated undermining of survival paths with nine repurposed drugs (CUSP9) by the International Initiative for Accelerated Improvement of Glioblastoma Care. *Oncotarget* 2013; 4: 502–30.
- 5 Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG. Inactivation of the DNA-repair gene *MGMT* and the clinical

- response of gliomas to alkylating agents. *N Engl J Med* 2000; 343: 1350–4.
- 6 Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R. *MGMT* gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; 352: 997–1003.
 - 7 Barker CA, Bishop AJ, Chang M, Beal K, Chan TA. Valproic acid use during radiation therapy for glioblastoma associated with improved survival. *Int J Radiat Oncol Biol Phys* 2013; 86: 504–9.
 - 8 Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008; 455: 1061–8.
 - 9 Carrillo JA, Lai A, Nghiemphu PL, Kim HJ, Phillips HS, Kharbanda S, Moftakhar P, Lalaezari S, Yong W, Ellingson BM, Cloughesy TF, Pope WB. Relationship between tumor enhancement, edema, IDH1 mutational status, *MGMT* promoter methylation, and survival in glioblastoma. *Am J Neuroradiol* 2012; 33: 1349–55.
 - 10 Brennan CW, Verhaak RG, McKenna A, Campos B, Nounshmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, Beroukhi R, Bernard B, Wu CJ, Genovese G, Shmulevich I, Barnholtz-Sloan J, Zou L, Vegesna R, Shukla SA, Ciriello G, Yung WK, Zhang W, Sougnez C, Mikkelsen T, Aldape K, Bigner DD, Van Meir EG, Prados M, Sloan A, Black KL, Eschbacher J, Finocchiaro G, Friedman W, Andrews DW, Guha A, Iacocca M, O'Neill BP, Foltz G, Myers J, Weisenberger DJ, Penny R, Kucherlapati R, Perou CM, Hayes DN, Gibbs R, Marra M, Mills GB, Lander E, Spellman P, Wilson R, Sander C, Weinstein J, Meyerson M, Gabriel S, Laird PW, Haussler D, Getz G, Chin L; TCGA Research Network. The somatic genomic landscape of glioblastoma. *Cell* 2013; 155: 462–77.
 - 11 Visnyei K, Onodera H, Damoiseaux R, Saigusa K, Petrosyan S, De Vries D, Ferrari D, Saxe J, Panosyan EH, Masterman-Smith M, Mottahedeh J, Bradley KA, Huang J, Sabatti C, Nakano I, Kornblum HI. A molecular screening approach to identify and characterize inhibitors of glioblastoma stem cells. *Mol Cancer Ther* 2011; 10: 1818–28.
 - 12 Chae YK, Brown EN, Lei X, Melhem-Bertrandt A, Giordano SH, Litton JK, Hortobagyi GN, Gonzalez-Angulo AM, Chavez-Macgregor M. Use of ACE inhibitors and angiotensin receptor blockers and primary breast cancer outcomes. *J Cancer* 2013; 4: 549–56.
 - 13 Walsh EM, Kim R, Del Valle L, Weaver M, Sheffield J, Lazarovici P, Marcinkiewicz C. Importance of interaction between nerve growth factor and alpha9beta1 integrin in glial tumor angiogenesis. *Neuro Oncol* 2012; 14: 890–901.
 - 14 Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001; 95: 190–8.
 - 15 Emara M, Allalunis-Turner J. Effect of hypoxia on angiogenesis related factors in glioblastoma cells. *Oncol Rep* 2014; 31: 1947–53.
 - 16 Chim H, Armijo BS, Miller E, Gliniak C, Serret MA, Gosain AK. Propranolol induces regression of hemangioma cells through HIF-1alpha-mediated inhibition of VEGF-A. *Ann Surg* 2012; 256: 146–56.
 - 17 Spence AM, Muzi M, Swanson KR, O'Sullivan F, Rockhill JK, Rajendran JG, Adamsen TC, Link JM, Swanson PE, Yagle KJ, Rostomily RC, Silbergeld DL, Krohn KA. Regional hypoxia in glioblastoma multiforme quantified with [18F] fluoromisonidazole positron emission tomography before radiotherapy: correlation with time to progression and survival. *Clin Cancer Res* 2008; 14: 2623–30.
 - 18 Marampon F, Gravina GL, Zani BM, Popov VM, Fratticci A, Cerasani M, Di Genova D, Mancini M, Ciccarelli C, Ficorella C, Di Cesare E, Festuccia C. Hypoxia sustains glioblastoma radioresistance through ERKs/DNA-PKcs/HIF-1alpha functional interplay. *Int J Oncol* 2014; 44: 2121–31.
 - 19 Hsieh CH, Lee CH, Liang JA, Yu CY, Shyu WC. Cycling hypoxia increases U87 glioma cell radioresistance via ROS induced higher and long-term HIF-1 signal transduction activity. *Oncol Rep* 2010; 24: 1629–36.
 - 20 Amberger-Murphy V Hypoxia helps glioma to fight therapy. *Curr Cancer Drug Targets* 2009; 9: 381–90.
 - 21 Liang BC. Effects of hypoxia on drug resistance phenotype and genotype in human glioma cell lines. *J Neurooncol* 1996; 29: 149–55.
 - 22 Levkovitz Y, Gil-Ad I, Zeldich E, Dayag M, Weizman A. Differential induction of apoptosis by antidepressants in glioma and neuroblastoma cell lines: evidence for p-c-Jun, cytochrome c, and caspase-3 involvement. *J Mol Neurosci* 2005; 27: 29–42.
 - 23 Sachlos E, Risueno RM, Laronde S, Shapovalova Z, Lee JH, Russell J, Malig M, McNicol JD, Fiebig-Comyn A, Graham M, Levadoux-Martin M, Lee JB, Giacomelli AO, Hassell JA, Fischer-Russell D, Trus MR, Foley R, Leber B, Xenocostas A, Brown ED, Collins TJ, Bhatia M. Identification of drugs including a dopamine receptor antagonist that selectively target cancer stem cells. *Cell* 2012; 149: 1284–97.
 - 24 Walker AJ, Grainge M, Bates TE, Card TR. Survival of glioma and colorectal cancer patients using tricyclic antidepressants post-diagnosis. *Cancer Causes Control* 2012; 23: 1959–64.
 - 25 Higgins SC, Pilkington GJ. The *in vitro* effects of tricyclic drugs and dexamethasone on cellular respiration of malignant glioma. *Anticancer Res* 2010; 30: 391–7.
 - 26 Tzadok S, Beery E, Israeli M, Uziel O, Lahav M, Fenig E, Gil-Ad I, Weizman A, Nordenberg J. *In vitro* novel combinations of psychotropics and anti-cancer modalities in U87 human glioblastoma cells. *Int J Oncol* 2010; 37: 1043–51.
 - 27 Yde CW, Clausen MP, Bennetzen MV, Lykkesfeldt AE, Mouritsen OG, Guerra B. The antipsychotic drug chlorpromazine enhances the cytotoxic effect of tamoxifen in tamoxifen-sensitive and tamoxifen-resistant human breast cancer cells. *Anticancer Drugs* 2009; 20: 723–35.
 - 28 Kast RE, Ellingson BM, Marosi C, Halatsch ME. Glioblastoma treatment using perphenazine to block the subventricular zone's tumor trophic functions. *J Neurooncol* 2014; 116: 207–12.

- 29 de Jonge J, Berghauer Pont LM, Idema S, Kloezeman JJ, Noske D, Dirven CM, Lamfers ML. Therapeutic concentrations of anti-epileptic drugs do not inhibit the activity of the oncolytic adenovirus Delta24-RGD in malignant glioma. *J Gene Med* 2013; 15: 134–41.
- 30 Bobustuc GC, Baker CH, Limaye A, Jenkins WD, Pearl G, Avgeropoulos NG, Konduri SD. Levetiracetam enhances p53-mediated MGMT inhibition and sensitizes glioblastoma cells to temozolomide. *Neuro Oncol* 2010; 12: 917–27.
- 31 Camphausen K, Cerna D, Scott T, Sproull M, Burgan WE, Cerra MA, Fine H, Tofilon PJ. Enhancement of *in vitro* and *in vivo* tumor cell radiosensitivity by valproic acid. *Int J Cancer* 2005; 114: 380–6.
- 32 Chinnaiyan P, Cerna D, Burgan WE, Beam K, Williams ES, Camphausen K, Tofilon PJ. Postradiation sensitization of the histone deacetylase inhibitor valproic acid. *Clin Cancer Res* 2008; 14: 5410–5.
- 33 Jaeckle KA, Ballman K, Furth A, Buckner JC. Correlation of enzyme-inducing anticonvulsant use with outcome of patients with glioblastoma. *Neurology* 2009; 73: 1207–13.
- 34 Oberndorfer S, Piribauer M, Marosi C, Lahrman H, Hitzemberger P, Grisold W. P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy. *J Neurooncol* 2005; 72: 255–60.
- 35 Weller M, Gorlia T, Cairncross JG, van den Bent MJ, Mason W, Belanger K, Brandes AA, Bogdahn U, Macdonald DR, Forsyth P, Rossetti AO, Lacombe D, Mirimanoff RO, Veitch CJ, Stupp R. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. *Neurology* 2011; 77: 1156–64.
- 36 Ghodke-Puranik Y, Thorn CF, Lamba JK, Leeder JS, Song W, Birnbaum AK, Altman RB, Klein TE. Valproic acid pathway: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics* 2013; 23: 236–41.
- 37 Eyal S, Yagen B, Sobol E, Altschuler Y, Shmuel M, Bialer M. The activity of antiepileptic drugs as histone deacetylase inhibitors. *Epilepsia* 2004; 45: 737–44.
- 38 van Nifterik KA, Van den Berg J, Slotman BJ, Lafleur MV, Sminia P, Stalpers LJ. Valproic acid sensitizes human glioma cells for temozolomide and gamma-radiation. *J Neurooncol* 2012; 107: 61–7.
- 39 Gupta PP, Thacker AK, Haider J, Dhawan S, Pandey N, Pandey AK. Assessment of topiramate's efficacy and safety in epilepsy. *J Neurosci Rural Pract* 2014; 5: 144–8.
- 40 Vajda FJ, Graham J, Roten A, Lander CM, O'Brien TJ, Eadie M. Teratogenicity of the newer antiepileptic drugs – the Australian experience. *J Clin Neurosci* 2012; 19: 57–9.
- 41 Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014; 261: 579–88.
- 42 Ma B, Xiang Y, Li T, Yu HM, Li XJ. Inhibitory effect of topiramate on Lewis lung carcinoma metastasis and its relation with AQP1 water channel. *Acta Pharmacol Sin* 2004; 25: 54–60.
- 43 Ma B, Pan Y, Song Q, Tie L, Zhang Y, Xiao Y, Zhang J, Han J, Xu Y, Xiang Y, Yu HM, Li XJ. The effect of topiramate on tumor-related angiogenesis and on the serum proteome of mice bearing Lewis lung carcinoma. *Eur J Pharmacol* 2011; 663: 9–16.
- 44 Cemeus C, Zhao TT, Barrett GM, Lorimer IA, Dimitroulakos J. Lovastatin enhances gefitinib activity in glioblastoma cells irrespective of EGFRvIII and PTEN status. *J Neurooncol* 2008; 90: 9–17.
- 45 Chan DY, Chen GG, Poon WS, Liu PC. Lovastatin sensitized human glioblastoma cells to TRAIL-induced apoptosis. *J Neurooncol* 2008; 86: 273–83.
- 46 Yanae M, Tsubaki M, Satou T, Itoh T, Imano M, Yamazoe Y, Nishida S. Statin-induced apoptosis via the suppression of ERK1/2 and Akt activation by inhibition of the geranylgeranyl-pyrophosphate biosynthesis in glioblastoma. *J Exp Clin Cancer Res* 2011; 30: 74.
- 47 Yongjun Y, Shuyun H, Lei C, Xiangrong C, Zhilin Y, Yiquan K. Atorvastatin suppresses glioma invasion and migration by reducing microglial MT1-MMP expression. *J Neuroimmunol* 2013; 260: 1–8.
- 48 Gabrys D, Dorfler A, Yaromina A, Hessel F, Krause M, Oertel R, Baumann M. Effects of lovastatin alone or combined with irradiation on tumor cells *in vitro* and *in vivo*. *Strahlenther Onkol* 2008; 184: 48–53.
- 49 Wu H, Jiang H, Lu D, Xiong Y, Qu C, Zhou D, Mahmood A, Chopp M. Effect of simvastatin on glioma cell proliferation, migration, and apoptosis. *Neurosurgery* 2009; 65: 1087–96; discussion 96–7.
- 50 Tapia-Perez JH, Kirches E, Mawrin C, Firsching R, Schneider T. Cytotoxic effect of different statins and thiazolidinediones on malignant glioma cells. *Cancer Chemother Pharmacol* 2011; 67: 1193–201.
- 51 Wood WG, Eckert GP, Igbavboa U, Muller WE. Statins and neuroprotection: a prescription to move the field forward. *Ann N Y Acad Sci* 2010; 1199: 69–76.
- 52 Engineer DR, Burney BO, Hayes TG, Garcia JM. Exposure to ACEI/ARB and beta-blockers is associated with improved survival and decreased tumor progression and hospitalizations in patients with advanced colon cancer. *Transl Oncol* 2013; 6: 539–45.
- 53 Arrieta O, Guevara P, Escobar E, Garcia-Navarrete R, Pineda B, Sotelo J. Blockage of angiotensin II type I receptor decreases the synthesis of growth factors and induces apoptosis in C6 cultured cells and C6 rat glioma. *Br J Cancer* 2005; 92: 1247–52.
- 54 Juillerat-Jeanneret L, Celerier J, Chapuis Bernasconi C, Nguyen G, Wostl W, Maerki HP, Janzer RC, Corvol P, Gasc JM. Renin and angiotensinogen expression and functions in growth and apoptosis of human glioblastoma. *Br J Cancer* 2004; 90: 1059–68.
- 55 Rivera E, Arrieta O, Guevara P, Duarte-Rojo A, Sotelo J. AT1 receptor is present in glioma cells; its blockage reduces the growth of rat glioma. *Br J Cancer* 2001; 85: 1396–9.
- 56 Rooprai HK, Kandaneeratchi A, Maidment SL, Christidou M, Trillo-Pazos G, Dexter DT, Rucklidge GJ, Widmer W,

- Pilkington GJ. Evaluation of the effects of swainsonine, captopril, tangeretin and nobiletin on the biological behaviour of brain tumour cells *in vitro*. *Neuropathol Appl Neurobiol* 2001; 27: 29–39.
- 57 Kast RE, Halatsch ME. Matrix metalloproteinase-2 and -9 in glioblastoma: a trio of old drugs-captopril, disulfiram and nelfinavir-are inhibitors with potential as adjunctive treatments in glioblastoma. *Arch Med Res* 2012; 43: 243–7.
- 58 Cardwell CR, Mc Menamin UC, Hicks BM, Hughes C, Cantwell MM, Murray LJ. Drugs affecting the renin-angiotensin system and survival from cancer: a population based study of breast, colorectal and prostate cancer patient cohorts. *BMC Med* 2014; 12: 28.
- 59 Holmes S, Griffith EJ, Musto G, Minuk GY. Antihypertensive medications and survival in patients with cancer: a population-based retrospective cohort study. *Cancer Epidemiol* 2013; 37: 881–5.
- 60 Carpentier AF, Ferrari D, Bailon O, Ursu R, Banissi C, Dubessy AL, Belin C, Levy C. Steroid-sparing effects of angiotensin-II inhibitors in glioblastoma patients. *Eur J Neurol* 2012; 19: 1337–42.
- 61 Petty A, Myshkin E, Qin H, Guo H, Miao H, Tochtrop GP, Hsieh JT, Page P, Liu L, Lindner DJ, Acharya C, MacKerell AD Jr, Ficker E, Song J, Wang B. A small molecule agonist of EphA2 receptor tyrosine kinase inhibits tumor cell migration *in vitro* and prostate cancer metastasis *in vivo*. *PLoS One* 2012; 7: e42120.
- 62 Lamy S, Lachambre MP, Lord-Dufour S, Beliveau R. Propranolol suppresses angiogenesis *in vitro*: inhibition of proliferation, migration, and differentiation of endothelial cells. *Vascul Pharmacol* 2010; 53: 200–8.
- 63 Larochelle P, Tobe SW, Lacourciere Y. Beta-blockers in hypertension: studies and meta-analyses over the years. *Can J Cardiol* 2014; 30: S16–22.
- 64 Pasquier E, Ciccolini J, Carre M, Giacometti S, Fanciullino R, Pouchy C, Montero MP, Serdjebi C, Kavallaris M, Andre N. Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. *Oncotarget* 2011; 2: 797–809.
- 65 Pasquier E, Street J, Pouchy C, Carre M, Gifford AJ, Murray J, Norris MD, Trahair T, Andre N, Kavallaris M. Beta-blockers increase response to chemotherapy via direct antitumour and anti-angiogenic mechanisms in neuroblastoma. *Br J Cancer* 2013; 108: 2485–94.
- 66 Zhang D, Ma Q, Shen S, Hu H. Inhibition of pancreatic cancer cell proliferation by propranolol occurs through apoptosis induction: the study of beta-adrenoceptor antagonist's anticancer effect in pancreatic cancer cell. *Pancreas* 2009; 38: 94–100.
- 67 Kozanoglu I, Yandim MK, Cincin ZB, Ozdogu H, Cakmakoglu B, Baran Y. New indication for therapeutic potential of an old well-known drug (propranolol) for multiple myeloma. *J Cancer Res Clin Oncol* 2013; 139: 327–35.
- 68 Yang EV, Sood AK, Chen M, Li Y, Eubank TD, Marsh CB, Jewell S, Flavahan NA, Morrison C, Yeh PE, Lemeshow S, Glaser R. Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res* 2006; 66: 10357–64.
- 69 Miller SC, Huang R, Sakamuru S, Shukla SJ, Attene-Ramos MS, Shinn P, van Leer D, Leister W, Austin CP, Xia M. Identification of known drugs that act as inhibitors of NF-kappaB signaling and their mechanism of action. *Biochem Pharmacol* 2010; 79: 1272–80.
- 70 Kang KB, Wang TT, Woon CT, Cheah ES, Moore XL, Zhu C, Wong MC. Enhancement of glioblastoma radioresponse by a selective COX-2 inhibitor celecoxib: inhibition of tumor angiogenesis with extensive tumor necrosis. *Int J Radiat Oncol Biol Phys* 2007; 67: 888–96.
- 71 Kesari S, Schiff D, Henson JW, Muzikansky A, Gigas DC, Doherty L, Batchelor TT, Longtine JA, Ligon KL, Weaver S, Laforme A, Ramakrishna N, Black PM, Drappatz J, Ciampa A, Folkman J, Kieran M, Wen PY. Phase II study of temozolomide, thalidomide, and celecoxib for newly diagnosed glioblastoma in adults. *Neuro Oncol* 2008; 10: 300–8.
- 72 Sesen J, Dahan P, Scotland SJ, Saland E, Dang VT, Lemarie A, Tyler BM, Brem H, Toulas C, Cohen-Jonathan Moyal E, Sarry JE, Skuli N. Metformin inhibits growth of human glioblastoma cells and enhances therapeutic response. *PLoS One* 2015; 10: e0123721.
- 73 Wan Z, Shi W, Shao B, Shi J, Shen A, Ma Y, Chen J, Lan Q. Peroxisome proliferator-activated receptor gamma agonist pioglitazone inhibits beta-catenin-mediated glioma cell growth and invasion. *Mol Cell Biochem* 2011; 349: 1–10.
- 74 Hori YS, Hosoda R, Akiyama Y, Sebori R, Wanibuchi M, Mikami T, Sugino T, Suzuki K, Maruyama M, Tsukamoto M, Mikuni N, Horio Y, Kuno A. Chloroquine potentiates temozolomide cytotoxicity by inhibiting mitochondrial autophagy in glioma cells. *J Neurooncol* 2015; 122: 11–20.
- 75 Golden EB, Cho HY, Jahanian A, Hofman FM, Louie SG, Schonthal AH, Chen TC. Chloroquine enhances temozolomide cytotoxicity in malignant gliomas by blocking autophagy. *Neurosurg Focus* 2014; 37: E12.
- 76 Paranjpe A, Zhang R, Ali-Osman F, Bobustuc GC, Srivenugopal KS. Disulfiram is a direct and potent inhibitor of human O6-methylguanine-DNA methyltransferase (MGMT) in brain tumor cells and mouse brain and markedly increases the alkylating DNA damage. *Carcinogenesis* 2014; 35: 692–702.
- 77 Dey M, Ulasov IV, Lesniak MS. Virotherapy against malignant glioma stem cells. *Cancer Lett* 2010; 289: 1–10.
- 78 Solomon IH, Ramkissoon SH, Milner DA Jr, Folkerth RD. Cytomegalovirus and glioblastoma: a review of evidence for their association and indications for testing and treatment. *J Neuropathol Exp Neurol* 2014; 73: 994–8.