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Drug Repurposing in Medulloblastoma: Challenges and Recommendations

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Opinion statement

Medulloblastoma is the most frequently diagnosed primary malignant brain tumor among children. Currently available therapeutic strategies are based on surgical resection, chemotherapy, and/or radiotherapy. However, majority of patients quickly develop therapeutic resistance and are often left with long-term therapy-related side effects and sequelae. Therefore, there remains a dire need to develop more effective therapeutics to overcome the acquired resistance to currently available therapies. Unfortunately, the process of developing novel anti-neoplastic drugs from bench to bedside is highly time-consuming and very expensive. A wide range of drugs that are already in clinical use for treating non-

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cancerous diseases might commonly target tumor-associated signaling pathways as well and hence be of interest in treating different cancers. This is referred to as drug repurposing or repositioning. In medulloblastoma, drug repurposing has recently gained a remarkable interest as an alternative therapy to overcome therapy resistance, wherein existing non-tumor drugs are being tested for their potential anti-neoplastic effects outside the scope of their original use.

Introduction

Medulloblastoma (MB) is the most frequently diagnosed primary malignant brain tumor diagnosed in children [1], accounting for around a quarter of all pediatric central nervous system (CNS) neoplasms [2]. It is a highly aggressive tumor that usually develops early during embryonic life [3•]. It mainly originates from the cerebellar vermis and thus primarily affects children in their first year of life [4]. Studies have shown that MB arises from remnants of the primitive neuroectoderm within the germinal matrix of the fourth ventricle roof [5,6] or from the external granular layer precursor cells [7,8].

It is approximated that MB affects around 3.9 per million children aged less than 19 years old [9], and it affects males more than females [9]. Although MB is aggressive and highly invasive, the 10-year survival rate is around 60–70% [9] and the 5-year survival rate ranges between 70 and 85% [10,11] due to the multimodality treatment approach and improved treatments methods [5]. Nevertheless, there still exists an imbalance in survival rates where low- to middle-income countries record 33% [12] to 45.6% [13] 5-year progression-free survival rates.

Classification of medulloblastoma subtypes

Histological classification of medulloblastoma

According to the World Health Organization (WHO), MB can be either classified based on a histological classification or according to molecular and genetic features. Histologically, MB can be divided into four distinct subsets [14]: classic MB (CMB), desmoplastic/nodular MB (DMB), MB with extensive nodularity (MBEN), and large cell/anaplastic with subgroups of melanotic MB and medullomyoblastoma which are extremely rare [15]. CMB represents the most common histological subtype of MB and is characterized by sheets of densely packed basophilic small round cells with high nuclear-to-cytoplasmic ratio and showing a mitotic and apoptotic activity [14]. Similar to CMB, MBEN shows small round tumor cells but is associated with reticulin-free islands within a reticulin-rich stroma [16,17]. This subtype is also accompanied by a favorable prognosis [16]. As for DMB, what distinguishes this subtype from CMB is the presence of desmoplasia and marked tendency for neuronal differentiation [18]. Considering the large cell/anaplastic MB, it is a highly aggressive tumor subtype that is usually located in the cerebellar vermis. Tumor cells show extensive and marked nuclear pleomorphism with prominent nucleoli [18].

Molecular classification of medulloblastoma

At the molecular level, according to the latest consensus nomenclature, 4 major subgroups of MB were identified [19]: $MB^{WNT\text{-}activated}$, $MB^{SHH\text{-}activated,TP53\text{-}mutant}$, $MB^{SHH\text{-}activated,TP53\text{-}wildtype}$, and $MB^{non\text{-}WNT/non\text{-}SHH}$. The latter comprises two subgroups, $MB^{non\text{-}WNT/non\text{-}SHH,\ Group\text{-}3}$ [20,21] and $MB^{non\text{-}WNT/non\text{-}SHH,\ Group\text{-}4}$ [22,23], which are characterized by high rates of disseminated disease and less understood pathology [24•].

WNT-activated medulloblastoma

The WNT subgroup is the mostly known subgroup, with the best long-term prognosis and survival rates that exceed 90% compared to other molecular subgroups [25]. $MB^{WNT\text{-}activated}$ harbors activating mutations in the Wnt pathway effector β-catenin 1 (*CTNNB1*) [26,27] and is characterized by positive nuclear immunohistochemical (IHC) staining for β-catenin [28], *AXIN1* mutation and *AXIN2* deletion [29], and loss of chromosome 6 (monosomy six) [30,31] which is considered a defining feature of this MB subgroup that is rarely found in non-WNT MB tumors [32].

SHH-activated medulloblastoma

Regarding the SHH subgroup, it is most common in infants and adults. SHH-activated MB constitutes 30% of all MB cases and is further subdivided into *TP53*-mutant and *TP53*-wildtype [33]. It has a good prognosis in infants and is usually caused by aberrant activation of the sonic hedgehog signaling pathway [34]. Infantile MB can be due to germline mutations of the Shh negative regulator *SUFU*. Somatic mutations, as in *PTCH*, *SMO*, and *SUFU*, and even amplification of *GLI1* and *GLI2* were also observed in this MB subgroup [35,36,32,37]. As for identification methods, immunohistochemical staining for SFRP1 or GAB1, in addition to the deletion of chromosome 9q, is considered to be limited to SHH-MB (the gene for *PTCH* is located on the chromosome 9q22) [32].

Non-*WNT*/non-*SHH* medulloblastoma

The non-*WNT*/non-*SHH* MB group is subdivided into *groups 3* and *4*, both of which have moderately high overall expression of *MYCN* [38]. *NPR3* has been postulated to be a potential molecular marker for $MB^{non\text{-}WNT/non\text{-}SHH,\ Group\text{-}3}$, while *KCNA1*, *CDK6*, and *MYCN* marker genes characterize $MB^{non\text{-}WNT/non\text{-}SHH,\ Group\text{-}4}$ [39]. In general, unlike the other groups, group 3 is the most common type in infants and is associated with a very poor prognosis [32]. In non-*WNT*/non-*SHH* MB *groups 3* and *4*, *H3K27me3* is recurrently dysregulated. Normally, *H3K27* is methylated by a methyltransferase EZH2 and demethylated by demethylase 6A (KDM6A) and KDM6B. KDM6A and other members of the KDM family were found to be mutated in both *groups 3* and *4*. Besides, EZH2 overexpression and gain of 7q (where *EZH2* is located) were observed in these subgroups. Henceforth, disruption of genes in cooperation with histone methylation might represent major events leading to tumor development [40–42].

Current treatment modalities for medulloblastoma:

Different treatment modalities are currently in use clinically for MB ranging from surgical intervention to chemotherapy and radiation therapy [43,44]. Those therapeutic options, however, are accompanied with substantial adverse effects including, for instance, 7–50% increased risk of postoperative cerebellar mutism syndrome (pCMS) following surgery [45–47]. Also, although craniospinal radiotherapy prolongs patient survival, it decreases patients' intelligence quotient (IQ) by 2–4 points per year [48] and is accompanied by other toxicities like impaired spinal growth and endocrine dysfunction [49]. Despite that surgery remains the major therapeutic option to remove the malignant mass, radiotherapy is used to destroy tumor cells via proton therapy, and chemotherapy is also given in single-drug or combinatorial approaches [50]. Other treatments are also available that include molecular targeted therapies, such as silencing endogenous miRNA or targeting specific pathways that underlie MB initiation and growth [51].

Despite the available therapies, MB like many other CNS tumors [52,3] recurs in many patients pertaining to development of therapeutic resistance, which necessitates looking for more effective treatments [53]. Recently, a promising approach has emerged which enables the usage of non-cancerous approved drugs that commonly target specific cancer-related pathways, for cancer [54••]. This approach is known as drug repurposing or repositioning and serves as a potential novel option for treating different tumors and overcoming therapy resistance.

Repurposing approved drugs in cancer

Repurposing drugs in cancer via experimental and computational approaches

Despite the advancement in cancer research, developing anti-tumor therapies is still very challenging due to the different stages that any drug needs to pass through before approving it for clinical use and more importantly due to development of therapeutic resistance. Therefore, new approaches are required to tackle this issue. Drug repurposing is a promising approach recently emerging across different tumor types where existing drugs are being used beyond their original non-cancer indications to be utilized in cancer therapy. Repositioning of FDA-approved drugs for new clinical indications offers advantages of reduced drug development time and cost [55], taking into consideration that pharmacokinetic, pharmacodynamic, and toxicological data have been already assessed [56]. Drug repurposing has been effective in different oncologic conditions. Anthracyclines, for instance, are class of antibiotics including doxorubicin, daunorubicin, epirubicin, and idarubicin that have been shown to instigate chemotherapeutic potentials in various tumor types such as breast cancer [57,58] and lymphoma [59,60].

Repurposing FDA-approved drugs usually requires combining both experimental (in vitro and in vivo screening of the potential drugs [61]) and computational "in silico" approaches (computationally determine drug interactions with specific targets [62]). In the pediatric population, children with brain tumors have not shown a significant improvement in their survival [63], raising

the need for identifying more effective drugs to improve patients' quality of life and prolong survival [64,54••,65]. In this review, we summarize the drug repurposing approaches that have been described so far in MBs (Table 1).

Overcoming the challenges in crossing the blood-brain barrier

The blood-brain barrier (BBB) comprises highly specialized microvascular endothelial cells [66] that are characterized by specific properties such as lack of fenestration, tight junctions, and presence of solute carriers and transporters [67]. It is implicated in the maintenance of brain homeostasis and protecting the brain tissue from different substances, toxins, and pathogens [68]. Brain tumors recruit the vascular network of the brain for their continuous growth; however, the BBB hinders delivery of some drugs to the tumor site in the brain [69], particularly some chemotherapeutic agents that are too large or hydrophilic to cross it [70,71]. Different factors compromise the drugs' ability to reach the brain, such as efflux pumps (P-glycoprotein) that actively transport drugs back into the blood [72], physiochemical properties of drugs [73], and the glymphatic system [74,75].

MB is subcategorized into different subgroups possessing distinct genomic profiles [76]. Recently, it was declared that the MB genotype dictates the phenotype of BBB, explaining the disparate prognoses pertaining to the differential chemotherapeutic responsiveness seen between the various MB subtypes [77]. For example, while $MB^{WNT\text{-}activated}$ has an unfunctional BBB rendering it more vulnerable to chemotherapy, $MB^{SHH\text{-}activated}$ has an intact BBB [77]. This heterogeneity in the BBB phenotypes among the different MB subgroups raises a need for identifying novel therapeutic targets and trying new drugs to improve the management of MB. Using non-cancer drugs that have already gained FDA approval and trying them as potential anti-cancer therapies for MB might be a possible option to bypass the timely stages of drug testing needed. Those drugs include antihyperlipidemic agents, medications used for cardiovascular diseases, anthelmintic drugs, antimicrobials, antivirals and antiretroviral drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), medicines used in neurological disorders, and others as outlined below.

Drug repurposing in medulloblastoma

Lipid-lowering agents

Statins are frequently prescribed drugs for the treatment of high cholesterol levels in the blood [78]. Studies have reported anti-tumor effects of statins and decreased cancer-related mortality among patients with different tumor types who are taking statins; hence, they have been proposed for drug repurposing studies [79]. Statins are effective competitive inhibitors of β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase [80], which is a key enzyme in the cholesterol synthesis pathway [81,82]. Inhibition of HMG-CoA reductase via statins decreases production of mevalonate derivatives that are essential for many growth regulatory processes [83] such as proliferation, apoptosis, and differentiation [84].

Anti-cancer effects of lovastatin, a well-known and widely used statin, have been reported in many studies [85–87]. In one in vitro study, lovastatin induced apoptosis, reduced cell viability, and inhibited cell proliferation of MB cell lines

Table 1. Summary table of the drugs that have been repurposed to be used in medulloblastoma

Reference	Drug	Primary indication	BBB	Serious side effects	Safety in children	*In vitro* studies: MB cell lines used	*In vivo* studies: animal model used	Supposed mode of action in MB	Combination	Drug development	Effect
I- Lipid-lowering agents											
[1]	Lovastatin	Cholesterol-lowering drug/ prevents heart attack and stroke	Yes	Breathing troubles, fast heartbeat, heartburn…	For children ≥8 years	Daoy; D283MED, D341MED; UW228		• Inhibition of HMG-CoA reductase	0	1	• Induced morphological changes in MB cells • Induced apoptosis • Enhanced DNA degradation • Reduced cell viability and cell numbers • Inhibited cell proliferation
[2]	Lovastatin	Cholesterol-lowering drug/ prevents heart attack and stroke	Yes	Breathing troubles, fast heartbeat, heartburn…	For children ≥8 years	Daoy; D283MED; D341MED; UW228		• Inhibition of HMG-CoA reductase	0	1	• Induced morphological changes in MB cells (shrinkage) • Induced apoptosis • Induced DNA fragmentation (laddering)
[3]	Lovastatin	Cholesterol-lowering drug/ prevents heart attack and stroke	Yes	Breathing troubles, fast heartbeat, heartburn…	For children ≥8 years	Daoy; D283MED; D341MED		• Inhibition of HMG-CoA reductase • Modulation of gene expression ($P21^{WAFI}$ and $P27^{KIP1}$)	0	1	• Inhibited MB cell growth • Induced apoptosis • Decreased cell proliferation
[4]	Lovastatin	Cholesterol-lowering drug/ prevents heart attack and stroke	Yes	Breathing troubles, fast heartbeat, heartburn…	For children ≥8 years	Daoy; D283MED; UW228	Daoy/D283 orthotropic MB xenografted mice	• Modulation of gene expression (upregulation of miR-33b; downregulation of c-Myc)	0	1/2	• Arrested cell cycle • Decreased cell proliferation • Increased apoptosis • Reduced tumor growth and invasion in vivo • Improved survival of mice bearing tumor
[5]	Simvastatin	Cholesterol and triglycerides lowering drug/ prevents heart attack and stroke	Yes	Rare interstitial lung disease, and cognitive impairment (memory loss)	For children ≥10 years	Daoy; D283MED; D341MED		• Inhibition of HMG-CoA reductase • Activation of Caspase 3/7/8 and 9 • Alteration of Bcl-2 family protein expression	0	1	• Induced apoptosis in MB cell

Table 1. (continued)

[6]	Simvastatin	Cholesterol and triglycerides lowering drug/ prevents heart attack and stroke	Yes	Rare interstitial lung disease, and cognitive impairment (memory loss)	For children ≥10 years	MB cells isolated from Ptch1$^{+/-}$ mouse	Ptch1$^{+/-}$ MB allografted CB17/SCID mice	• Inhibition of HMG-CoA reductase • Inhibition of HH signaling	1-With vismodegib	1/2	• Decreased cell proliferation *in vitro* • Decreased tumor growth and volume *in vivo* • Promoted MB cell differentiation • Increased apoptosis • Inhibited HH-MB progression
[6]	Atorvastatin	LDL lowering drug/ prevents heart attack and stroke	Yes	Rare Rhabdomyolysis, confusion and memory loss	Safe at 5-40 mg		Ptch1$^{+/-}$ MB allografted CB17/SCID	• Inhibition of HMG-CoA reductase • Inhibition of HH signaling	1-with vismodegib	2	• Suppressed MB growth
[7]	Fenofibrate	Cholesterol lowering drug/ arteriosclerosis drug	Yes. But in a low rate	Rare gallstones, liver problems, persistent vomiting and unusual muscle pain, blood clots and pancreatitis	Recommended dose is one capsule (67 mg/day/20 Kg body weight	DsB8 mouse MB; D384MED; Daoy		• Activation of PPAR-mediated transcriptional activity • Inhibition of IGF-I-mediated phosphorylation cascade	0	1	• Decreased cell proliferation • Inhibited cell growth • Induced morphological changes • Induced apoptosis • Arrested cell cycle • Inhibition of clonogenic growth • Inhibition of colony formation
II- Cardiac glycosides											
[8]	Digoxin	Heart failure and atrial fibrillation drug	Yes	Rare severe vomiting, allergic reaction and breathing troubles	The dose depends on age and on the serum level of digoxin	MED8A; D283MED	NOD.129S7(B6)-Rag1^{tm1Mom}/J severe immunodeficient SCID mice	• Modulation of ERK/AKT signaling	2	0, 1/2	• Decreased cell viability • Prolonged survival *in vivo* • Increased apoptosis
[8]	Proscillaridin	Heart failure drug	Yes	Rare Disorientation, mental confusion, acute psychoses, convulsion, and blurred vision	Not safe. Two-third of pediatric patients have long-term adverse effects from treatment	MED8A; D283MED		• Modulation of Erk/ Akt signaling	0	1	• Decreased cell viability

Table 1. (continued)

[9]	Ouabain	Heart failure drug	Cannot easily cross BBB so its pharmacological action is more peripheral	Signs after acute overdose include cardiac arrhythmias, heart block, and pulse irregularities	Should not be administrated to children under 6 months. The recommended dose for children is an age-dependent	Daoy		• Inhibition of EGF signaling	0	1	• Induced cellular stress in MB cells • Induced morphological changes • Prevented the formation of actin stress fibers • Prevented EGF-induced cell migration • Inhibited cell motility in wound healing assay
III- Other cardiovascular disease drugs:											
[10]	Verapamil	Anti-hypertension drug, angina and ischemic myocardium drug	Yes	Severe dizziness, very low heartbeat. Rarely liver damage and continuous vomiting	The dose depends on the weight	TE671		• Inhibition of calcium channel • Inhibition of ABC transporter	0	1	• Inhibited cell proliferation • Inhibition of cell growth • Slight cell cycle arrest at G1 phase but considerable arrest at S and G2-M phases
[11]	Verapamil	Anti-hypertension drug, angina and ischemic myocardium drug	Yes	Severe dizziness, very low heartbeat. Rarely liver damage and continuous vomiting	The dose depends on the weight	Daoy; UW228; Fresh MB tissues from patients at the time of surgery	Daoy cells xenografted mice	• Inhibition of ABC transporter	2	1/2	• Enhanced sensitization of MB cells to radiation • Reduced proliferation *in vitro* • Reduced tumorigenicity of MB *in vivo*
[12]	Propranolol	Anti-hypertension and myocardial infraction drug	Yes	Rare bronchiolitis, cool extremities and sleep disturbance	Not safe	Daoy		• Inhibition of β-adrenergic receptor • Inhibition of MMP-9	0	1	• Decreased cell proliferation
[6]	Triparanol	Cholesterol-lowering drug	Yes	Hair loss, Vision loss and atherosclerosis	Not safe	MB cells isolated from Ptch1$^{+/-}$ mouse		• Inhibition of HMG-CoA reductase • Inhibition of HH signaling	0	1	• Decreased MB cell proliferation

Table 1. (continued)

IV- Anthelminthic drugs											
[13]	Pyrvinium	Anti-pinworm drug	Yes	Blue or purple skin, weight gain, shortness of breath	Safe in effective doses (dose depends on body weight). Caution is recommended in children < 10 Kgs	NIH-3T3; HEK293T; Light-II	Ptch+/− allografted CD-1 nude mice	• Inhibition of HH signaling pathway	0	1/2	• Reduced MB growth *in vivo* • Reduced tumor size • Decreased number of tumor cells
[14]	Mebendazole	Whipworm, horse pinworm, roundworm and hookworm drug	Yes	No	It is recommended for children > 2 years in a specific dose	D425MED; UW228	Ptch+/− , p53−/− allografted athymic nude mice, D425 xenografted mice	• Inhibition of VEGFR2 kinase	0	1/2	• Competed with ATP in VEGFR2 tyrosine kinase reaction • Inhibited tumor growth • Improved the survival *in vivo* • Reduced angiogenesis • Reduced tubulin polymerization in UW228 MB cells
[15]	Mebendazole	Whipworm, horse pinworm, roundworm and hookworm drug	Yes	No	It is recommended for children > 2 years in a specific dose	D425	D425 xenografted mice	• Inhibition of VEGFR2 kinase	3-with elacridar	1/2	• Improved survival of brain tumor-bearing mice
[16]	Mebendazole	Whipworm, horse pinworm, roundworm and hookworm drug	Yes	No	It is recommended for children > 2 years in a specific dose	Daoy; Light2 cells, NIH3T3 cells	Daoy orthotopic MB xenografted mice	• Inhibition of HH signaling	1-with vismodegib	1/2	• Suppressed tumor growth • Inhibited HH-dependent cell proliferation • Decreased cell viability • Enhanced survival *in vivo* • Increased apoptosis
[17]	Nifurtimox	Trypanosoma cruzi (Chagas disease)	Yes	Dizziness, weight loss, confusion, tremor …	Safety is dose-dependent	Daoy; D283MED		• Activation of Nrf2 pathway • Activation of caspase-3 • Increased ROS level	3-With tetrathiomolybdate		• Inhibition of MB cell growth • Decreased cell viability • Induced apoptosis • Induced cytotoxicity • Enhanced oxidative stress

Table 1. (continued)

V- Antimicrobial drugs											
[18]	Salinomycin	Anti-coccidial drug	Yes	Neurotoxic side effects	Not safe	Daoy; D425MED; D283MED		• Modulation of protein expression (PDGFRβ, MYC, P21 and Bcl-2) • Suppression of Notch signaling	0	1	• Suppressed MB cell proliferation • Increased cellular death • Disrupted cell cycle • Cytotoxic effect
[19]	Itraconazole	Anti-fungal drug	It has poor permeability across BBB	Signs of cognitive heart failure, confusion, blurred vision and loss of bladder control	Safe for children. However, it may harm unborn infants	Shh-Light2, SmoA1-Light, Ptch−/− MEF; NIH-3T3 cells HEK 293S	Ptch+/− mice; p53−/− mice (allografted with primary MB)	• Inhibition of HH pathway and Smo antagonist	3- with Cyclopamine	1/2	• Inhibited growth of MB allograft
VI- Antiviral/antiretroviral drugs											
[20]	Valganciclovir	Anti-viral drug	It has poor permeability across BBB	Rare mood changes and seizure ….	The rate of certain adverse reactions is more frequent in pediatric patients than in adults	D324MED; D283MED; UW228-3	D283MEB xenografted NMRI *nu/nu* mice	• Inhibition of DNA polymerases	3- with celecoxib	1/2	• Inhibited MB tumor cell growth *in vitro* and *in vivo* • Reduced the clonogenic and tumorigenic capacity of MB cells • Reduced PGE_2 production
[21]	Abacavir	Antiretroviral (Anti-HIV) drug	Yes	Hypersensitivity reactions and predisposition to developing cardiovascular diseases	WHO Recommended it for children < 3 years	Daoy; D283MED		• Inhibition of Telomerase	0	1	• Induced senescence in MB cell lines • Decreased growth and promoted differentiation of MB cells • Decreased cell density • Induced cellular death • Decreased cellular proliferation

Table 1. (continued)

VII- NSAIDs											
[20]	Celecoxib	Osteoarthritis, rheumatoid arthritis, acute pain in adults…	Yes	Serious stomach and intestinal ulcer and signs of heart stroke or attack	Yes	D324MED; D283MED; UW228-3	D283MEB xenografted NMRI *nu/nu* mice	• Inhibition of Cox-2	3- with valganciclovir	1/2	• Inhibited MB tumor growth *in vitro* and *in vivo* • Reduced the clonogenic and tumorigenic capacity of MB cells • inhibited PGE2 synthesis
[22]	Celecoxib	Osteoarthritis, rheumatoid arthritis, acute pain in adults…	Yes	Serious stomach and intestinal ulcer and signs of heart stroke or attack	Yes	Daoy (CD133/Nestin DPs; CD133/Nestin DNs)	MB-DPs and MB-DNs xenografted immunocompromised mice	• Inhibition of STAT3 pathway • Downregulation of STAT3-related protein (JAK2, Bcl2, c-MYC)	2	1/2	• Suppressed tumorigenesis *in vivo* • Induced apoptosis • Decreased cell viability • Enhanced radiosensitivity • Enhanced the loss of cancer stem-like gene signatures • Enhanced differentiation of tumor cells • Decreased colony and sphere formation
[23]	Celecoxib	Osteoarthritis, rheumatoid arthritis, acute pain in adults…	Yes	Serious stomach and intestinal ulcer and signs of heart stroke or attack	Yes	Daoy; UW228	MB-CD133^{+} grafted SCID mice (BALB/c stain)	• Inhibition of COX-2	2	1/2	• Decreased the viability of MB cells • Induced apoptosis • Reduced colony formation • Decreased angiogenesis gene expression and stem cell markers • Decreased tumor volume *in vivo* • Improved radiosensitivity
[24]	Celecoxib	Osteoarthritis, rheumatoid arthritis, acute pain in adults…	Yes	Serious stomach and intestinal ulcer and signs of heart stroke or attack	Yes	D283MED; D324MED; PFSK-1; DAOY; MEB-MED-8A; D425MED; D458MED, D384MED; UW228-3	D283MED xenografted NMRI nu/nu mice	• Inhibition of COX-2	0	1/2	• Inhibited PGE2 • Decreased cell viability • Inhibited colony formation • Induced apoptosis • Inhibited tumor growth and reduced tumor volume *in vivo* • Decreased angiogenesis

Table 1. (continued)

[24]	Diclofenac	Moderate pain, symptoms of osteoarthritis and rheumatoid arthritis	Yes	Liver damage, low blood pressure, congestive heart failure	Relatively safe in children	D283MED; D324MED; PFSK-1; DAOY; MEB-MED-8A; D425MED; D458MED, D384MED; UW228 3	D283MED xenografted NMRI nu/nu mice	• Inhibition of COX-1 and COX-2	0	1/2	• Decreased level of PGE_2 *in vitro* • Decreased cell viability • Inhibition of colony formation • Induced apoptosis • Inhibited tumor growth and reduced tumor volume *in vivo* • Arrested cell cycle • Decreased angiogenesis
[25]	Tolfenamic acid	Pain of migraine headache	Yes	Peptic ulcers, GI bleeding, hypersensitivity reactions, hypertension and cardiac failure …	Dosage has not yet been established, and the use is not recommended in children	Daoy; D283MED	D283MEB xenografted athymic nude mouse	• Inhibition of COX-2 • Inhibition of Sp1 and survivin expression	0	1/2	• Inhibited MB cell proliferation and growth • Decreased cell viability • Reduced tumor volume • Induced apoptosis in MB cells
[26]	Flurbiprofen	Arthritis pain relief	Low permeability	signs of an allergic reaction, signs of a heart attack or stroke, liver problems and stomach bleeding…	Not recommended for use in children < 12 years	Daoy; TE671		• Inhibition of cyclin B • Increase of P53 expression	0	1	• Inhibited cellular proliferation • Disrupted cell cycle progression

Table 1. (continued)

VIII- Drugs used for neurological disorders											
[27]	Thioridazine	Antipsychotic drug (Schizophrenia)	Yes	Uncontrolled muscle movements, tremor, confusion, seizure …	Thioridazine should not be used to treat conditions in children	Daoy; Vandy-MB-11; Math1-Cre; SmoM2; $Ptch1^{-/-}$; $p53^{-/-}$ cells.	C283 MB and Vandy-MB-11 xenografted mice $Ptch^{+/-}$; Math1-SB11; T2Onc2 Sleeping Beauty mouse model	• Blockage of EAG2 channel	0	1/2, 3 (case report)	• Reduced MB growth and metastasis *in vivo* • Reduced tumorigenicity • Impaired MB cell rear retraction, migratory polarization and motility and velocity *in vitro*
[28]	Valproic acid	Antipsychotic drug (anti-seizure and antidepressant, anti-convulsant)	Yes	Rare trembling, chest pain, blurred vision, weight gain and liver failure …	High risk of liver damage are children <2 years	Daoy, D283MED; ONS-76		• Inhibition of HDAC • Modulation of gene expression	1- with cisplatin (CDDP)	1	• Reduced cell viability
[29]	Valproic acid	Antipsychotic drug (anti-seizure and antidepressant, anti-convulsant)	Yes	Rare trembling, chest pain, blurred vision, weight gain and liver failure …	High risk of liver damage are children <2 years	Daoy; D283MED	Daoy and D283MED xenografted SCID mice	• Inhibition of HDAC • Inhibition of c-MYC gene expression • Hyperacetylation of histone H3 and H4 • Modulation of gene expression	0	1/2	• Inhibited cell proliferation and tumor growth • Induced cell cycle arrest and apoptosis • Induced senescence in MB cells • Induced differentiation of tumor cells • Inhibited tumorigenicity
[30]	Lithium	Antipsychotic drug (Bipolar disorder)	Yes	Neurotoxic side effects	Safe at low dose for treatment in children with intellectual disability and bipolar disorder	Daoy; D283MED		• Inactivation of GSK-3ß	0	1	• Decreased cell proliferation • Decreased metabolic activity • Arrested cell cycle progression • Increased cell mortality (non-apoptotic cell death)

Table 1. (continued)

[31]	Lithium	Antipsychotic drug (Bipolar disorder)	Yes	Neurotoxic side effects	Safe at low dose for treatment in children with intellectual disability and bipolar disorder	Wild type *TP53* cell lines (ONS76; D283MED; MEB-MED-8A); *TP53* mutant cell lines (UW228; Daoy)		• Inhibition of GSK-3ß • Activation of Wnt	2	1	• Sensitized TP53 mutant MB to radiation
[32]	Sertraline, chlorprothixene, and Chlorpromazine	Antipsychotic drugs (antidepressant, schizophrenia and bipolar disorder)	Yes	Yes. Chest pain, tachycardia, severe dizziness, weight gain….	for patients >18 years	Daoy		• Inhibition of REST/NRSE-mSin3 interaction	0	0-1	• Inhibited MB cell growth • Inhibited sphere formation
IX- Dermatological drugs											
[33]	13-cis-retinoic acid	Acne treatment	Yes	Yes. Rare pancreatitis, mood changes, depression, hearing loss…	Safety has not been established. The dose must be determined by the doctor	D283MED; ND2:SmoA1 transgenic mouse lines	D283 MB xenografted nu/nu athymic mice	• Activation of BMP-2	1-with SAHA	1/2	• Induced apoptotic cell death • Decreased cell viability • Decreased tumor volume in vivo
[34]	13-cis-retinoic acid	Acne treatment	Yes	Yes. Rare pancreatitis, mood changes, depression, hearing loss…	Safety has not been established. The dose must be determined by the doctor	Daoy; UW228; D283MED; D341MED;	D283 MB xenografts in athymic nude mice	• Activation of BMP-2	0	1/2	• Decreased tumor growth and size in vivo • Induced apoptosis • Induced differentiation of D283 cells

Table 1. (continued)

[35]	all-trans retinoic acid (ATRA)	Acne treatment	Yes	Serious allergic reaction, conjunctivitis, severe burning of the skin…	Safety is dose-dependent	Daoy; D283MED; D425MED; D458MED		• Activation of caspase-3/Poly (ADP-ribose) polymerase 1 pathway	0	1	• Decreased cell viability • Inhibited cell proliferation • Suppressed colony formation • Induced apoptosis • Enhanced MB cell differentiation
X- Other drugs											
[36]	Rapamycin	immunosuppressant drug	Yes	Yes. Oral ulcer, skin ulcer or sore, mole that leaks fluid or bleeds …	Safety is dose-dependent	Daoy		• Inhibition of mTOR	0	1	• Altered *pERK*, *pAKT* and *p-P27* activity • Decreased cell proliferation • Suppressed cell viability • Decreased cell migration
[37]	Fingolimod (FTY720)	Multiple sclerosis	Yes	Chest pain, fever, vision problems, dizziness…	Safe for children >10 years. However, cases of seizure were reported in 5.6% of fingolimod patients	D341MED; D384MED; D425MED	D425MED xenograft in athymic nude mice	• Activation of PP2A • Downregulation of cyclin D1 • Generation of ROS • Inhibition of Sphk1	0	1/2	• Arrested cell cycle • Decreased cell viability and proliferation • Enhanced apoptosis • Decreased cell invasion and migration • Decreased tumor volume in vivo
[38]	17β-estradiol	atrophic vaginitis	Yes	cerebrovascular accident, myocardial infarction, fast heartbeat….	The safety in children has not been established and not indicated in prepubescent females. It increases the risk of birth defects.		Patched1 heterozygous ($Ptch1^{+/-}$) mice	• ERβ agonist	0	2	• Inhibited tumorigenesis and cell proliferation

Table 1. (continued)

[39]	17β-estradiol	atrophic vaginitis	Yes	cerebrovascular accident, myocardial infarction, fast heartbeat….	The safety in children has not been established and not indicated in prepubescent females. It increases the risk of birth defects.	Daoy; D283MED; PFSK1	D283MED xenograft in athymic nude mice	• ERβ agonist	0	1/2	• Stimulated MB growth and cellular migration • Increased the number of viable cells
[40]	17β-estradiol	atrophic vaginitis	Yes	cerebrovascular accident, myocardial infarction, fast heartbeat….	The safety in children has not been established and not indicated in prepubescent females. It increases the risk of birth defects.	Daoy; D283MED; UW228	D283MED xenograft mice	• ERβ agonist	0	1/2	• Did not affect MB cell proliferation
[41]	Sulfasalazine	Anti-rheumatic drug	Yes	Liver and kidney damage.	The safety in children < 2 has not yet been established.	Daoy; D283MED; D425MED		• Inhibition of NFκB	0	1	• Inhibition of MB cell growth

Table 1. (continued)

[42]	Phenformin	Anti-diabetic drug	Yes	Yes. Lactic acidosis,	Not available yet	Med1-MB cells; MB from Math1-CRE; $Ptch^{loxP/loxP}$ mice; Daoy	Math1-CRE; $Ptch^{loxP/loxP}$ mice; CD1-nude mice; NOD/SCID mice; C57BL/6J mice; Med1-MB allograft in SCID and CD1-nud mice; Math1-CRE; $PtchloxP^{loxP}$ allograft in SCID and CD1-nud mice	• Inhibition of mGPD • Inhibition of HH signaling	0	1/2	• Inhibition of MB cell growth • Decreased tumor volume in vivo • Decreased cellular proliferation
[43]	Disulfiram	Chronic alcoholic dependence	Yes	Cision changes, numbness, liver problems, mood changes, seizures….	The use and dose must be determined by a doctor	Daoy	Daoy MB xenograft mice	• Activation of oxidative stress • Loss of mitochondrial membrane integrity • Activation of MAPK pathway	0	1/2	• Induced apoptosis in vitro • Decreased cell viability and colony formation in vitro • Inhibiting tumor growth in vivo

Key for "Combination" column: "0" alone; "1" combined with chemotherapy; "2" combined with radiotherapy; "3" other combinations.
Key for "Drug development process" column: "0" *in silico* studies; "1" *in vitro* studies; "2" *in vivo* studies; "1/2" *in vitro* and *in vivo* studies; "3" clinical trials; "4" retrospective studies
Bcl-2, B cell lymphoma 2; BMP-2, bone morphogenic protein-2; COX-2, cyclooxygenase-2; EAG2 channel, ether-a-go-go 2 potassium channel; ERβ, estrogen receptor beta; GSK-3ß, glycogen synthase kinase-3; HDACi, histone deacetylate inhibitors; Hh, hedgehog pathway; MB, medulloblastoma; MB-DPs, MB-derived CD133/Nestin double-positive cells; MB-DNs, MB-derived CD133/Nestin double-negative cells; mGPD, mitochondrial glycerophosphate dehydrogenase; MMP-9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycin; NF B, nuclear factor Kappa-B; NSAIDs, non-steroidal anti-inflammatory drugs; P53, tumor suppressor gene; PGE2, prostaglandin E2; PDGFRβ, platelet-derived growth factor beta; PP2A, tumor suppressor protein phosphatase 2A; PPAR, peroxisome proliferator activated receptor; REST/NRSF, repressor-element 1 silencing transcription factor; SAHA, suberoylanilide hydroxamic acid; RSO, reactive oxygen species; SK3 channel, calcium-activated potassium-channel 3; Sp1, specificity protein 1 (transcription factor); Sphk1, sphingosine kinase 1; STAT3, signal transducer and activator of transcription 3; VEGFR2, vascular endothelial growth factor receptor 2

[88], and in another it induced DNA laddering and shrinkage of MB cells [83]. The anti-proliferative and apoptotic effects of lovastatin are mediated by modulation of $p27^{K1P1}$, *P53* and $p21^{WAF1}$ gene expression [89]. Takwi et al. also showed that lovastatin upregulates miR-33 gene expression, thus decreasing cell proliferation and inducing apoptosis in vitro, besides reducing tumor growth and improving survival in MB tumor-bearing mice in vivo [90].

Simvastatin, another antihyperlipidemic drug, was shown to induce apoptotic cell death in a time- and dose-dependent manner in MB cell lines in comparison to the control group via activation of different caspases (Caspase 3, 7, 8 and 9) and down-expression of anti-apoptotic Bcl-2 and Mcl-1 proteins [91]. An in vivo study revealed that simvastatin treatment of $Ptch1^{+/-}$ CB17/SCID mice repressed the Shh signaling pathway with a significant decline in glioma-associated oncogene 1 (Gli1) expression level in MB cells due to disruption of cholesterol biosynthesis [92]. In addition, simvastatin decreased the number of proliferating cells, reduced MB growth, induced apoptosis, and inhibited SHH-MB progression when combined with vismodegib [92].

In the same milieu, fenofibrate—which belongs to the "cholesterol-lowering drugs" family—is usually prescribed as a monotherapy for treating elevated triglyceride levels in patients with severe hypertriglyceridemia [93]. This drug was found to induce peroxisome proliferator activated receptor alpha (PPARα)–mediated cell cycle arrest and apoptosis in BsB8 mouse MB cell line as well as human MB Daoy and D283 cell lines [94]. Fenofibrate also inhibited IGF-I-induced phosphorylation events, which in turn attenuated the clonogenic growth of MB cells [94].

Cardiac glycosides

Cardiac glycosides (CGs) comprise a wide range of naturally derived steroid compounds prescribed for chronic heart failure [95]. They inhibit the enzyme sodium-potassium ATPase (Na^+/K^+-ATPase) [96,95] leading to depletion of potassium and raising sodium and calcium concentrations within cells [97]. Many studies investigated the anti-neoplastic effects of CGs mainly by inhibiting Na^+/K^+-ATPase [97,98]. CGs also exhibited antiproliferative and proapoptotic properties in tumor cells by activation of sarcoma (SRC) kinase and epidermal growth factor receptor (EGFR), prompting activation of mitogen-activated protein kinase (MAPK)-ERK1/2 signaling pathway and upregulating cell cycle inhibitor $P21^{CIP1}$ [99]. Moreover, a systematic in vivo study revealed that digoxin inhibits cell growth, induces apoptosis, and instigates modulation of gene expression related to ERK/AKT signaling pathway in groups 3 and 4 MB cell lines (MED8A and D283). It also significantly prolonged survival in orthotopic PDX mice models when combined with radiation therapy [100]. In the same study, proscillaridin, another CG, was reported to decrease cell viability in both group 3 and 4 MB cell lines (MED8A and D283) [100]. In the same milieu, Wolle *et al.* studied the interplay between ouabain and EGF signaling and demonstrated that this CG inhibits EGF-induced Erk1/2-Akt activation, and attenuated EGF-induced actin reorganization, prevented stress fiber formation, and inhibited MB cell motility [101].

Other cardiovascular disease drugs

Other medications used in heart diseases were also part of the repurposed drugs in MB. Verapamil, a calcium channel blocker (CCB) and ABC transporter inhibitor used in cardiovascular diseases, was reported to hinder cell viability and growth of TE671 human MB cell line [102] and inhibit xenograft tumor formation in vivo [103]. Propranolol, a β-adrenergic receptor blocker, was found to induce apoptosis and inhibit proliferation of MB cells by inhibiting Akt and Erk phosphorylation and MAPK signaling cascades [104]. Additionally, propranolol was shown to induce antiproliferative effects on Daoy MB cells due to the inhibition of PMP-induced MMP-9/Erk and I B phosphorylation [105].

Anthelminthic drugs

Anthelminthic drugs are widely used to treat parasitic worm infections [106]. Pyrvinium, prescribed to treat pinworm infections, was documented to inhibit *Wnt* [107] and *SHH* pathways [108] and decrease the expression of SHH markers, Gli1 and Ptch2 [109] besides reducing tumor growth and size of MB allograft [109]. Mebendazole, another antiparasitic drug, has recently been characterized by its anti-tumor properties via inhibition of a number of protein kinases [110] including vascular endothelial growth factor receptor 2 (VEGFR2) kinase activity in $Ptch^{+/-}$, $p53^{-/-}$ MB allograft [111,112]. It also improved survival and reduced tumor growth in tumor-bearing mice [113]. Another study by Bai et al. showed that combination therapy of elacridar and mebendazole polymorph C improved survival in D425 MB xenograft model [114]. The therapeutic effect of nifurtimox, another anthelmintic drug, was also tested in MB in combination with tetrathiomolybdate showing increased ROS cellular level in MB cell cultures [115].

Antimicrobial drugs

Antimicrobial drugs have gained considerable attention in cancer treatment. Adjuvant antimicrobial therapy is usually given to cancer patients prophylactically to prevent opportunistic infections by bacteria and viruses following chemotherapy due to immunosuppression [116]. Salinomycin, anticoccidial drug, is involved in treating many cancer types mainly by modulating Wnt, NF-B, and p38 MAPK signaling pathways [117–119]. It suppressed cell proliferation and metastasis, disrupted cell cycle progression, and induced cell death in MB cells by modulation of different proteins including MYC, PDGFRβ, Bcl-2, and p21 [120], besides suppressing Notch signaling [120] which is linked to the development and progression of MB [121]. Itraconazole, a commonly used anti-fungal drug [122], was also studied in MB revealing an inhibition in tumor growth in a mouse allograft model via suppression of the *SHH* pathway [47].

Antiviral/antiretroviral drugs

Antiviral drugs were also tested as antineoplastic agents due to their antiproliferative and cytotoxic properties [123]. Valganciclovir, anti-human cytomegalovirus (HCMV) drug, was shown to inhibit MB tumor growth in vitro and in vivo and reduce tumorigenic and clonogenic capacity of D324 MED, D283 MED, and UW228-3 cell lines by targeting DNA polymerases and decreasing prostaglandin E2 (PGE2) synthesis [124]. Abacavir (ABC), one of the most effective drugs for acquired immunodeficiency syndrome (AIDS) [125], is well

characterized by its telomerase inhibition activity and termination of DNA elongation [126]. Rossi et al. showed that abacavir treatment decreased cellular growth, disrupted cell cycle progression, and reduced proliferation of Daoy and D283MED MB cell lines [127]. Interestingly, both MB cell lines showed substantial senescence features after abacavir treatment [127].

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are highly selective cyclooxygenase (COX) inhibitors that suppress prostaglandin (PG) synthesis [128]. Recent studies have provided evidence that NSAIDs might serve as potential candidates for cancer treatment in various tumor types [129–134]. Celecoxib, a NSAID, has been used in many treatment protocols for pediatric tumors due to its anti-angiogenesis and immune-modulating effects [135]. It was shown to induce in vitro and in vivo anti-tumor effects in MB [124] via downregulating the expression of phosphorylated-STAT3 and STAT3-related genes (*JAK2*, *BCL2*, and *c-MYC*) [136]. It also enhanced the efficacy of radiotherapy [137] and synergistically improved survival of MB-bearing mice [136]. Noticeably, in vivo results indicated a potential role of celecoxib in inhibiting angiogenesis gene expression (*KDR*, *VEGFC* and *PDGFRA*) as well as stem cell genes (*Nestin*, *CD133*, *Sox-2*, *MSI1*, and *Bmi-1*) [137]. These potential effects of celecoxib in MB were also documented by Baryawno et al., suggesting the prospective benefit of celecoxib for treating patients with MB [138].

Diclofenac, another COX-1/COX-2 inhibitor, was shown to reduce cell viability, proliferation, and colony formation in vitro and to further decrease microvascular density and tumor size in vivo [138]. Tolfenamic acid, another NSAID, also caused a decrease in tumor weight and volume by about 40% in MB athymic nude mice model mediated by a decrease in targeting specificity protein 1 (Sp1) and survivin expression [139] that are implicated in cell proliferation, differentiation growth [140], and apoptosis [141] of MB. Another in vitro study investigated the effectiveness of NSAIDs as antitumor drugs and revealed that flurbiprofen treatment suppressed the growth of MB cells and disrupted cell cycle progression via modulating cyclin B and P53 protein expressions [142].

Drugs used for neurological disorders

Medications used in neurological disorders have recently gained huge popularity in oncology as treatment options for the complications resulting from cancer and its therapy among this population of patients [143] as well as being repurposed to treat the cancer itself [144,145]. Ether-a-go-go 2 (EAG2) potassium channels (which are present in brain regions [146]) are shown to be highly expressed in MB tissues and involved in MB development and progression [147] and hence are potential targets for the antipsychotic drug thioridazine (a potent EAG2 channel blocker) [148]. Additionally, valproic acid, a histone deacetylase inhibitor (HDACi), decreased cell viability of MB cell lines when combined with cisplatin (CDDP) [149] and reduced tumorigenicity in vivo at a clinically safe concentration [150]. The antitumor activity of valproic acid was associated with histone hyperacetylation (H3 and H4) and modulation of several genes expression (*P21*, *c-MYC*, *CDK4*, and *TP53*) [150].

Lithium has been characterized by neurotrophic effects and considered as a main therapeutic drug for the treatment of bipolar disorder [151,152]. It has profound effects on cell cycle, metabolism, and cell proliferation by which it potently inhibits cell cycle and accelerates cell death [153]. An in vitro study revealed that lithium targeted GSK3-β, slowed cell metabolic activity, arrested cell cycle, and induced non-apoptotic cell death in Daoy andD283 MB cell lines [154]. Another study documented that WNT activation by lithium improved the effect of radiotherapy in *TP53* mutant MB cells [155] suggesting a therapeutic property of lithium when combined with radiation for MB treatment but specifically for the *TP53*-mutant subgroup. Other antipsychotic medicines, such as sertraline, chlorprothixene, and chlorpromazine, were documented to inhibit MB cell growth and sphere formation in Daoy cells via inhibition of REST/NRSF-mSin3 interaction [156], raising the opportunity of new drug candidates for MB.

Dermatological drugs

Drugs used in dermatological diseases have also shown potential anti-tumor effects in MB. For instance, 13-cis retinoic acid, a dermatological drug, was shown to reduce cell viability and induce apoptosis via activating of bone morphogenetic protein-2 (BMP-2) synergistically with SAHA, a histone deacetylase inhibitor [157]. It also enhanced differentiation of D283 cells and reduced tumor volume in xenograft MB models [158]. All-*trans*-retinoic acid (ATRA) induced a dose-dependent decrease in cell viability and promoted apoptosis by activating caspase-3/poly(ADP-ribose) polymerase I effector pathway [159]. In addition, ATRA significantly inhibited cell and clonal proliferation and induced cellular differentiation of MB cells [159].

Other drugs

The antitumor effects of many other drugs were also studied in MB. Rapamycin, a well-known immunosuppressant drug, instigated a potent effect against cell proliferation and migration [160]. In other CNS tumors such as glioblastoma and neuroblastoma, rapamycin has proved to be effective in inducing anti-tumor effects in vitro, by targeting a cancer stem cell (CSC) subpopulation of cells [161]. In MB, treatment of Daoy cell lines with rapamycin showed a marked anti-tumor effects via inhibition of mTOR signaling [162]. Fingolimod, another immunosuppressant drug used in multiple sclerosis, was reported to have a therapeutic potential in MB, where it arrested cell cycle, decreased viability and proliferation, and enhanced apoptosis of MB cells, besides decreasing tumor growth in vivo [163].

Unexpectedly, contradictory results were obtained following MB treatment with 17β-estradiol. Mancuso et al. showed an antiproliferative effect of 17β-estradiol in *Ptch1*-associated MB [164]. However, Belcher et al. documented the potential of estradiol to increase MB cell growth and migration [165], whereas 17β-estradiol treatment did not affect cell proliferation at any concentration tested in MB cell lines [166].

Sulfasalazine, an inhibitor of nuclear factor Kappa-B (NF B) signaling, was demonstrated to inhibit cell growth in MB cell lines [167]. The antitumor therapeutic effect of phenformin, an antidiabetic drug, was also tested in vitro and in vivo where phenformin treatment induced a significant inhibition of MB

cell growth and proliferation [168]. Interestingly, another antidiabetic medication metformin showed anti-tumor effects in glioblastoma and neuroblastoma CNS tumors via targeting CSCs in vitro [169].

Disulfiram, an FDA-approved drug for treatment of alcoholism [170], has been repurposed to study its anticancer effects owning to its multiple pharmacological mechanisms in targeting tumor cells and triggering oxidative stress [171], activating MAPK pathway [172], and suppressing the proteasome system [173]. In MB, disulfiram was shown to induce apoptosis and decrease cell viability and colony formation in Daoy cell line. It also induced a significant regression of tumor growth in MB xenografts [174].

Conclusions

In order to provide more comprehensive care for patients with cancer, it is crucial to decipher the mechanisms of action pertaining to the different drugs used clinically and understand the pleiotropic adverse effects and perspective interactions they might have with other medications. However, the dire need for developing and finding more efficient anti-tumor drugs urges the scientific society to change its approach towards seeking new strategies, most importantly via drug repurposing, to reach its goals in treating cancer patients and improving their quality of life. Repositioning previously FDA-approved drugs is indeed a promising strategy in cancer treatment particularly pediatric tumors owning to its various advantages including cost efficiency and shortened time-frame for safety pharmacology testing in drug development. At a clinical level, many FDA-approved drugs have been put under investigation in clinical trials on medulloblastoma patients [175], including anthelminthic drug "mebendazole" (ClinicalTrials.gov; phase I clinical trial; NCT02644291), cholinesterase inhibitor "donepezil" that is used to treat Alzheimer's disease (ClinicalTrials.gov; phase I clinical trial; NCT00452868), bradykinin B-2 receptor agonist "lobradimil" (ClinicalTrials.gov; phase II clinical trial; NCT00019422), and acetylcysteine, mannitol, and sodium thiosulfate (ClinicalTrials.gov; phase I clinical trial; NCT00238173).

Although treatment by repurposing drugs might seem to be a long way ahead to achieve, it carries potential hope for managing cancer in general and MB in particular. This novel therapeutic approach could help thousands of MB patients suffering worldwide and awaiting more efficient therapies to come up for their disease. Further experimental and clinical studies are needed to establish repurposed drugs as adjuvant remedies for MB and other tumors.

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Availability of data and material

Not applicable.

Code availability

Not applicable.

Authors' contributions

H.F. Bahmad and S. Nabha conceived the concept and idea of the present review. H.F. Bahmad and S. Nabha worked on the study design strategy and selected the topics to be discussed. H. Hammoud, Z. Saker, H.F. Bahmad, and S. Nabha did literature searches and screened titles and abstracts for relevance. H. Hammoud and Z. Saker abstracted the data from the eligible full text articles, analyzed and interpreted the data, and drafted the manuscript. H. Harati and Y. Fares revised the final draft of the manuscript. H.F. Bahmad and S. Nabha critically revised the manuscript with input from the entire team. All authors have read and approved the final draft.

Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interest.

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Not applicable.

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- •• Of major importance

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