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TITLE PAGE

Title: The role of germline variants in chemotherapy outcome in brain tumors: a systematic review of pharmacogenetic studies.

Running head: Pharmacogenetics of chemotherapy outcome in brain tumors.

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ABSTRACT

This systematic review provides an overview of publications concerning pharmacogenetic research in pediatric patients with medulloblastoma and low-grade glioma. Three electronic databases searches including a manual search were performed to identify studies investigating potential interactions between germline variants and chemotherapy efficacy and toxicity. Of 3,570 citations, twenty-one studies were included. Outcomes include overall survival, progression-free survival and treatment related adverse events (*N* = 5), cisplatin-induced ototoxicity (*N* = 13) and vincristine-induced neurotoxicity (*N* = 3). This review shows that the number of pharmacogenetic studies in well-defined pediatric brain tumor cohorts is poor and studies often report conflicting results. Large-scale international collaborations allowing analysis of sufficiently sized cohorts are therefore very important for the future of personalized medicine in brain tumors.

INTRODUCTION

Brain tumors are the most common solid malignancies of childhood, with incidence rates of 3-5 per 100,000 children per year in the western population.[1, 2] The majority of pediatric brain tumors are low-grade gliomas and medulloblastomas.[3] Low-grade gliomas (WHO-classification grade I and II) derive from glial cells in the central nervous system and are considered less aggressive with favorable survival rates of 85-95%.[4] Medulloblastomas are primary neuroectodermal tumors with survival rates varying between 30% and 80%, depending on risk group and age.[5-9] Despite these types of brain tumors to be clinically very different, they are treated with comparable chemotherapeutic regimens, including the cornerstone agents cisplatin, carboplatin, vincristine and cyclophosphamide. Unfortunately, brain tumor patients often suffer from long term sequelae partly due to tumor specific features like location and size, and partly due to treatment related side effects.

Chemotherapy made it possible in several treatment protocols to postpone radiotherapy or decrease its dose or target volume, thereby decreasing radiotherapy side effects and, furthermore, increase survival.[10, 11] Despite the advances of chemotherapy, patients show a great variety in response to chemotherapeutic agents. Not only concerning anti-tumor effect, but also in the development and severity of toxicities. Chemotherapy-related side effects play a major role in reduced quality of life.[12] The most disabling long-term side effects caused by the chemotherapy include ototoxicity, nephrotoxicity, decreased cognitive functions and neurotoxicity.[13, 14] Ototoxicity is most often caused by treatment with cisplatin or carboplatin, which can result in an impairment of daily functioning and cognitive development.[15, 16] In addition, these platinum-based agents can, especially when combined with cyclophosphamide, lead to an increased risk of nephrotoxicity. Vincristine, a drug commonly used in pediatric cancer practice, is known to induce serious peripheral neurotoxicity during treatment. Severe toxicities are still often a reason for chemotherapy dose adjustments, which leads to a reduction of the desired anti-tumor effect and, consequently, might influence treatment efficacy.

Efforts have been made to reduce the toxic side effects of chemotherapy in children to prevent them from long-term sequelae. For example, amifostine addition may be protective against cisplatin-induced ototoxicity.[17, 18] However, due to the lack of large randomized controlled trials testing its protective effect and a meta-analysis reporting no statistically significant results, amifostine is not included in clinical guidelines.[19] Clinical differences, e.g. age and cumulative chemotherapy dose, are known to play a role in the variable response to chemotherapy, but do not sufficiently predict the occurrence of severe side effects.[20, 21] For this reason, no clinical or biological markers for chemotherapy response are available for upfront stratification of patients with a brain tumor. Gaining more insight in the cause of the variations in response to chemotherapy and being able to predict response might help to optimize chemotherapeutic treatment for these patients and might prevent them from low treatment efficacy and drug-related adverse events. A tool to gain this insight is pharmacogenetics.

Pharmacogenetic studies aim to identify inherited germline genetic markers that are associated with drug response, including treatment efficacy and drug-related adverse events. Associations found in pharmacogenetic research can be used for creating predictive models, offering tailored therapy and might thereby lead to improved survival and prevention from severe toxicities. This study field has already shown promising results in oncology patients. For example, multiple pharmacogenetic studies have shown a link between variants in the *DPYD* gene and high risk of severe toxicities during treatment with fluoropyrimidines, one of the most frequently prescribed group of anticancer drugs.[22-24] In the field of pediatric oncology, genetic variants associated with the outcome of acute lymphoblastic leukemia (ALL) are extensively investigated. An example is the role of polymorphisms in the glutathione-*S* transferase family, e.g. *GSTM1*, in the response to chemotherapy in treatment of ALL.[25] Pharmacogenetic studies have been published investigating patients with other types of cancer being exposed to the same chemotherapeutic agents as brain tumor patients, e.g. vincristine in ALL patients.[26] However from a pharmacogenetic view, brain tumors distinguish

themselves from other pediatric cancers because of the presence of multiple possible confounding factors. These factors may include for example hearing loss secondary to cranial radiotherapy and decreased cognitive function as a result of tumor localization and size. Also, chemotherapeutic regimens (including cumulative dose) do often vary depending on the type of cancer. Therefore, it might be difficult to directly translate the findings to other (pediatric) cancer patients to brain tumor patients.

This systematic review is a collection of pharmacogenetic studies investigating the response to chemotherapy in pediatric patients with a medulloblastoma or low-grade glioma. This review provides an overview of the current state of studies in this research area and may present a more distinct lead for future studies.

MATERIALS AND METHODS

Studies were included if they investigated associations between germline polymorphisms and treatment outcome of chemotherapy in medulloblastoma and low-grade glioma patients. The cornerstone agents used in current treatment regimens, being cisplatin, carboplatin, vincristine and cyclophosphamide, plus the additional agents etoposide and lomustine were included in the search. Treatment outcome was defined as chemotherapy efficacy, being overall survival (OS) or progression free survival (PFS), or chemotherapy-related toxicity. Studies investigating the mentioned chemotherapeutic agents in heterogeneous cohorts with multiple pediatric cancers including brain tumors were also selected. Studies in patients with an anaplastic glioma (grade III) or glioblastoma (grade IV) were excluded, because of treatment regimens with other chemotherapeutic agents.

The electronic databases MEDLINE, Embase, and Cochrane Library were systematically searched for relevant publications without limitations concerning publication dates. This was performed with the help of a medical librarian. The date of search was 30th of October, 2016. Detailed search terms are presented in ***Supplementary Table 1***. Two reviewers (MK and MC) independently screened the list of citations for eligible articles. Potential citations were reviewed by their titles; selected titles were reviewed by abstract and, if the abstract was eligible, by full-text. After systematic screening, the reference lists of the included articles were manually screened for additional potential articles that may have been missed with the initial search strategy. Discrepancies between the two reviewers concerning eligibility of the studies did not occur. Case reports, conference abstracts and articles not written in English were excluded, as well as studies investigating associations with genetic variants in tumor cells.

RESULTS

The systematic search yielded a total of 3,570 unique citations, of which twenty-one studies were included in the review (***Figure 1***). The majority of the included studies used a candidate gene approach. Also, one pathway approach study and one genome-wide association study (GWAS) were identified. Pharmacogenetic studies regarding carboplatin, cyclophosphamide, etoposide and lomustine were not found. The included studies could be sorted into three categories; studies investigating the role of variants in overall treatment outcome of patients with brain tumors and studies specifically looking into relations between inherited variants and cisplatin-induced ototoxicity and vincristine-induced neurotoxicity. Here, the results of these studies will be presented and described by category.

Pharmacogenetics and overall treatment outcome

Five out of the twenty-one included studies focused on the role of pharmacogenetics with overall treatment outcome of chemotherapy in patients with medulloblastoma or low-grade glioma. Most studies investigated the influence of variations in specific genes on survival and presence of adverse events during treatment. It is important to note that treatment efficacy, e.g. OS and PFS, is not only determined by the chemotherapeutic treatment, but also by clinical variables, intrinsic tumor characteristics and other treatment facets. Despite this fact, survival is often used as an endpoint in pharmacogenetic studies into chemotherapy outcome to assess the overall impact of a genetic variation on treatment efficacy. When a study is performed with candidate genes that are known to influence specific drug pharmacokinetics and -dynamics, one may suspect a relation between this genetic variant and a significant difference in treatment outcome. Details of the included studies are visualized in ***Table 1***, which shows that these candidate approach studies have mainly investigated detoxification genes.

Genetics variants in members of the glutathione *S*-transferase (*GST*) family are investigated in three studies, focusing on the relation of these variants with OS, PFS and risk of drug-related adverse events in brain tumor patients.[27-29] *GST* polymorphisms were studied because the enzymes encoded by these genes have a known function in detoxification of several types of chemotherapy, including alkylating and platinum agents, which are used in brain tumor treatment. A study in 42 medulloblastoma patients reported associations with both *GSTM1* and *GSTT1* null genotypes and any ≥grade 3 toxicity (including myelosuppression, neurotoxicity, ototoxicity and nephrotoxicity) and intellectual impairment.[28] Variants in *GST pi 1* (*GSTP1*) were studied in 106 medulloblastoma/PNET patients, identifying the variant *GSTP1* 105A>G to be significantly associated with hearing loss.[29] The mentioned associations in *GST* were not identified in an earlier study in a large cohort of various primary malignant gliomas (n=278, which consisted of forty-four low-grade gliomas, but zero medulloblastomas).[27] Replication studies concerning these associations in brain tumor patients have not appeared. No significant associations between variants in *GST* and PFS or OS were found in these studies.

Pharmacogenetics and cisplatin-induced ototoxicity

Thirteen papers reported on pharmacogenetics concerning cisplatin-induced hearing loss, including one GWAS, in a total of 649 brain tumor patients. An overview of the published articles is provided in ***Table 2***. The first published pharmacogenetic studies investigating cisplatin-induced ototoxicity in brain tumor patients were small-sized candidate approach studies in mixed cohorts of pediatric cancer patients.[30-33] Several *GST* variants were studied by Peters *et al*., leading to the identification of the association between *GSTM3*B* and a lower chance of cisplatin-induced ototoxicity in a small heterogeneous cancer cohort (n=39, of which 3 brain tumor patients).[30] These associations were never investigated in brain tumor patients only. Four studies, including one pathway approach study, investigated variants in the gene Megalin (*LRP2*), which was studied because of its known expression in the marginal cells of the stria vascularis in the inner ear.[33-36] The study by Riedemann *et al.* found an

association between the A allele of *LRP2* rs2075252 and a higher risk for development of ototoxicity in various pediatric cancer patients,[33] but this finding was not replicated by others.[34-36] Likewise, Choeyprasert *et al.* identified an association between *LRP2* rs2228171 and hearing loss, which was not in line results published in the other studies.[33-36]

Two newly investigated candidate genes, being *SLC22A2* and *SOD2,* were found to be significantly linked to ototoxicity. Lanvers-Kaminsky *et al*. found the polymorphism *SLC22A2* rs316019 G>T to be a protective marker for hearing loss in 64 pediatric patients (of which 12 brain tumor patients) and replicated this result in 66 adults with solid tumors.[37] The *SLC22A2* was studied because it encodes a transporter which is likely to be involved in cisplatin-induced oto- and nephrotoxicity. A study by Brown *et al*. recently reported the C allele of *SOD2* rs4880 to be significantly associated with increased susceptibility to ototoxicity in 71 medulloblastoma and PNET patients.[38] Five variants in this candidate gene were investigated because of their association with platinum toxicity in renal epithelial cells and its relation with noise-induced hearing loss. Replication studies of the results for *SLC22A2* and *SOD2* have not been published to date.

A pharmacogenetic study using a pathway approach was performed by Ross *et al.* in a cohort of 162 pediatric cancer patients, including 33 brain tumor patients.[35] The authors studied 1,949 variants in 220 drug metabolizing genes. The variants *TPMT* rs12201199 and *COMT* rs9332377 were detected to be significantly associated with cisplatin-induced hearing loss. The association between *TPMT* rs12201199 and hearing loss was replicated in a cohort consisting of 155 additional pediatric cancer patients (of which 37 brain tumor patients). Combined analysis of both patient groups also lead to an additional identification of an association between *ABCC3* rs1051640 and hearing loss.[39] However, the results of a study by Yang *et al*. were not in line with the previous findings, reporting no association of *TPMT* or *COMT* with ototoxicity, both *in vitro* (using mice with different *TPMT* genotypes) and *in vivo* (213 medulloblastoma patients).[40] Also, three recent publications were unable to detect

associated variants in *TPMT* and *COMT* to cisplatin-induced hearing loss in brain tumor patients.[36, 41, 42] The conflicting results of these studies suggest that these genetic variants may not be suitable for clinical application.

The only published GWAS in pediatric brain tumor patients so far was performed by Xu *et al.* in 2015. They investigated associations with 1,716,999 variants in 218 children with embryonal brain tumors, including 203 medulloblastoma patients.[41] The genetic variant rs1872328 in *ACYP2* reached genome-wide significance, showing patients who were carrying of the A allele of this variant all developed hearing loss. Similar results were found in the replication cohort which included 68 brain tumor patients.

Pharmacogenetics and vincristine-induced neurotoxicity

The role of genetic variants in the response to vincristine are only investigated in three small scale candidate gene studies in cohorts consisting of patients with various pediatric cancers, including a handful of brain tumor patients (***Table 3***). The studies investigated genetic variants in *ABCB1*, *CYP3A4* and *CYP3A5*, but they were unable to identify associations with vincristine pharmacokinetics and vincristine-induced neurotoxicity.[43-45]

DISCUSSION

This systematic review provides an overview of publications concerning pharmacogenetic research in pediatric medulloblastomas and low-grade gliomas, to evaluate existing evidence of the role of genetic variants to chemotherapy treatment outcome. As pharmacogenetics is poorly investigated in homogenous brain tumor populations, studies in pediatric solid tumor cohorts partially consisting of brain tumor patients were also reviewed. However, these results should be interpreted with caution, as interpatient variation concerning disease and treatment may be confounding variables for genetic association analysis, and thus may limit the predictive capacity of these variants in pediatric medulloblastomas and low-grade gliomas.

A few studies investigated the influence of genetic variants on survival as an endpoint for treatment efficacy. As mentioned before, survival is not only determined by chemotherapy efficacy, and therefore, in contrast to drug-related adverse events, other (clinical) variants need to be taken in great consideration when interpreting such an endpoint. Well-defined cohorts are therefore very important. Members of the detoxifying family *GST* have been a point of interest in pharmacogenetic studies in brain tumor patients concerning survival.[27-29] These genes encode for enzymes which catalyse the conjugation of glutathione of multiple toxic chemicals, which leads to inactivation. In other words, high GST enzyme activity is associated with drug resistance, which may lead to lower treatment efficacy and, consequently, lower survival rates. The drugs known to be influenced by *GST* members include alkylating and platinum agents and their metabolites, but also the free radicals formed by chemotherapy and radiation.[46, 47] Despite this hypothesis, genetic variants in *GST* genes did not significantly influence OS and PFS investigated in studies in low-grade gliomas and medulloblastomas.[27-29] One study included in this review did find a significant association between *GST* and survival. However the association was only present in the subgroup of anaplastic gliomas (WHO-classification grade III), which are treated with a different regimen compared to the brain tumors we focussed on.[27] Because of this difference, the results in anaplastic gliomas do probably not apply directly to low-grade gliomas and medulloblastomas.

The majority of pharmacogenetic studies in brain tumor patients have focussed on cisplatin-related ototoxicity. Cisplatin is a widely used chemotherapeutic agent in oncology, for treatment of e.g. pediatric brain tumors and osteosarcomas, and adult testicular, ovarian and non-small cell lung cancers. Especially children are at great risk of developing cisplatin-induced ototoxicity, which occurs in up to 60% of the pediatric patients.[48, 49] Brain tumor patients are even at higher risk, because the majority of these patients also receive cranial radiation, which is an additional risk factor for hearing loss.[50, 51] Because cisplatin is routinely used, numerous studies have appeared investigating prevention methods (e.g. medical interventions), as well as identification of clinical or genetic predictors to prevent this disabling side effect.[52] However to date, no upfront stratification methods for cisplatin-induced ototoxicity are used in daily practise.

Members of the *GST* family have not only been point of interest concerning their possible influence on treatment efficacy, but also their relation with cisplatin-induced ototoxicity. As mentioned earlier, GST enzymes are known to influence the level of drug resistance to platinum-based agents and have an effect on free radicals. Concerning ototoxicity, low GST activity is associated with low drug inactivation and thereby high levels of metabolites and free radicals, possibly leading to damage of the cochlea. One study in medulloblastoma patients reported that carriers of the G allele on position 105 in the coding sequence of *GSTP1* have an increased risk of hearing loss after cisplatin treatment.[29] In contrast, Oldenburg *et al*. found an increased risk of ototoxicity in patient carrying the A allele in this *GSTP1* variant in 173 adult testicular cancer survivors.[53] Also, no associations with genetic variants in *GSTP1* were identified in three studies in pediatric solid cancers (including the pathway approach study by Ross *et al*.).[30, 35, 36] However, the majority of patients in these cohorts did not receive cranial radiation, which is a confounding factor for ototoxicity and, therefore, might influence the results of the genetic association analysis. The earlier mentioned GWAS, also performed in medulloblastomas patients, does not report this polymorphism to be associated with cisplatin-induced hearing loss.[41]

A variant in the gene *ACYP2* seems very promising to predict cisplatin induced hearing loss, which was discovered in a GWAS in medulloblastoma patients by Xu *et al.*[41] In this study, all patients carrying the A allele in rs1872328 developed hearing loss upon cisplatin treatment. The exact working mechanism of the variant is no elucidated yet, but *ACYP2* is known to be expressed in the cochlea.[54] Nonetheless, this is in our view a promising candidate for clinical implementation as in our replication study in osteosarcoma patients, again all patients with the A allele developed hearing loss. These findings suggest that the variant might also be useful to predict cisplatin-induced hearing loss in other tumors treated with this agent.[55] Unfortunately, the frequency of the variant is not high, thus only a small part of the patients that have a high risk for hearing loss can be identified.

The polymorphisms *TPMT* and *COMT* and their role in cisplatin-induced hearing loss have been extensively studied in pediatric oncology patients, including brain tumor patients. Due to inconsistent results of multiple study groups, the effect of these variants is still controversial.[35, 36, 39-42, 56] These inconsistencies could be a result of differences in for example audiometry or study population and thereby, findings are not generally applicable. In addition, the direct mechanism between these variants and ototoxicity is still unclear, which makes it difficult to value the findings thus far.

The role of pharmacogenetics in vincristine, known for its high risk of neurotoxicity, is poorly investigated in brain tumor patients, despite the fact that it is often the reason for chemotherapy dose limitations in these patients. Pharmacogenetic studies to vincristine-induced toxicities have been more extensively performed in patients with ALL, leading to the identification of the relation between *CYP3A5* and vincristine-induced neurotoxicity.[57, 58] However, other studies failed to confirm these findings,[26, 59, 60] including studies in solid tumors discussed in this review.[44, 45]

Recently, a GWAS by Diouf *et al.* identified a polymorphism in the promoter region of the gene *CEP72* associated with an increased risk on and severity of vincristine-related neurotoxicity in

321 patients with ALL.[26] The results were backed-up with *in vitro* experiments showing an influence of *CEP72* expression on the neurons and leukemia cells derived from human stem cells and their sensitivity to vincristine. These results were replicated in adult ALL patients, but no associations were found in a study in a Spanish cohort with pediatric ALL patients.[61, 62] However, the mentioned studies investigated neurotoxicity development during different treatment phases, being during the continuation and induction phase, respectively. To date, no publications focussing on *CEP72* polymorphisms and its role in the development of vincristine-induced toxicities in brain tumor patients have appeared. Because it is hypothesised that the potential interaction between the germline *CEP72* polymorphisms and vincristine is comparable in different cancer types, it would be very interesting to perform replication studies in other vincristine-treated malignancies, including brain tumors. Because vincristine is a widely used agent, this might lead to a broad clinical application of these findings.

Concluding remarks

This review revealed that the pharmacogenetic research area in brain tumors is mainly performed in heterogeneous pediatric cancer cohorts. In contrast to other pediatric malignancies including osteosarcoma and ALL [55, 63], the number pharmacogenetic studies in well-defined cohorts of exclusively brain tumor patients is poor. Without a homogeneous study population and validation of findings in a sufficiently large population, clinical implementation of pharmacogenetic results is not within reach yet. Though we believe that the *ACYP2* and *CEP72* genes are very good candidates to study in additional patient cohorts with the ultimate goal, after proper validation, implementation in the clinical setting.

The majority of pharmacogenetic studies in brain tumors focused on one or a few candidate genes. A genome wide approach is an appropriate method to discover novel unexpected variants, but also to identify various variants which have limited effects on their own but together play a big role in final response to therapy. The number of GWASs is lagging behind

in the pediatric (brain) tumor population, considering the fact only one GWAS has been performed to date. This can probably be attributed to the small patient cohorts available for pharmacogenetic association studies. Large cohorts are required to create enough power to identify relevant variants using a GWAS, which emphasizes the need for national and international collaboration for brain tumor research. These homogeneous cohorts are not only needed for identification, but also for replication and (prospective) validation of associated genes, which are essential steps before clinical implementation is possible. In addition, the pharmacogenetic field is also moving to next generation sequencing to identify genetic variants or mutations linked to treatment outcome, for which large cohorts are even more essential. Sufficiently sized cohorts and large scale screening methods will result in more insight in interpatient treatment variability, and may lead to clinical application of pharmacogenetic knowledge. Preferably, genetic association results should be backed-up with functional studies to unravel the working mechanisms of the findings. Of course, not the complete spectrum of treatment outcome can be predicted by pharmacogenetics. Also tumor properties (e.g. somatic mutations or tumor methylation patterns) can be the reason for a poor outcome. Ultimately, these factors in combination with pharmacogenetics will enable optimal personalized treatment of pediatric brain tumor patients, which should be reflected in improved survival and less side-effects.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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FIGURES AND TABLES

Figure 1: Flowchart of study selection

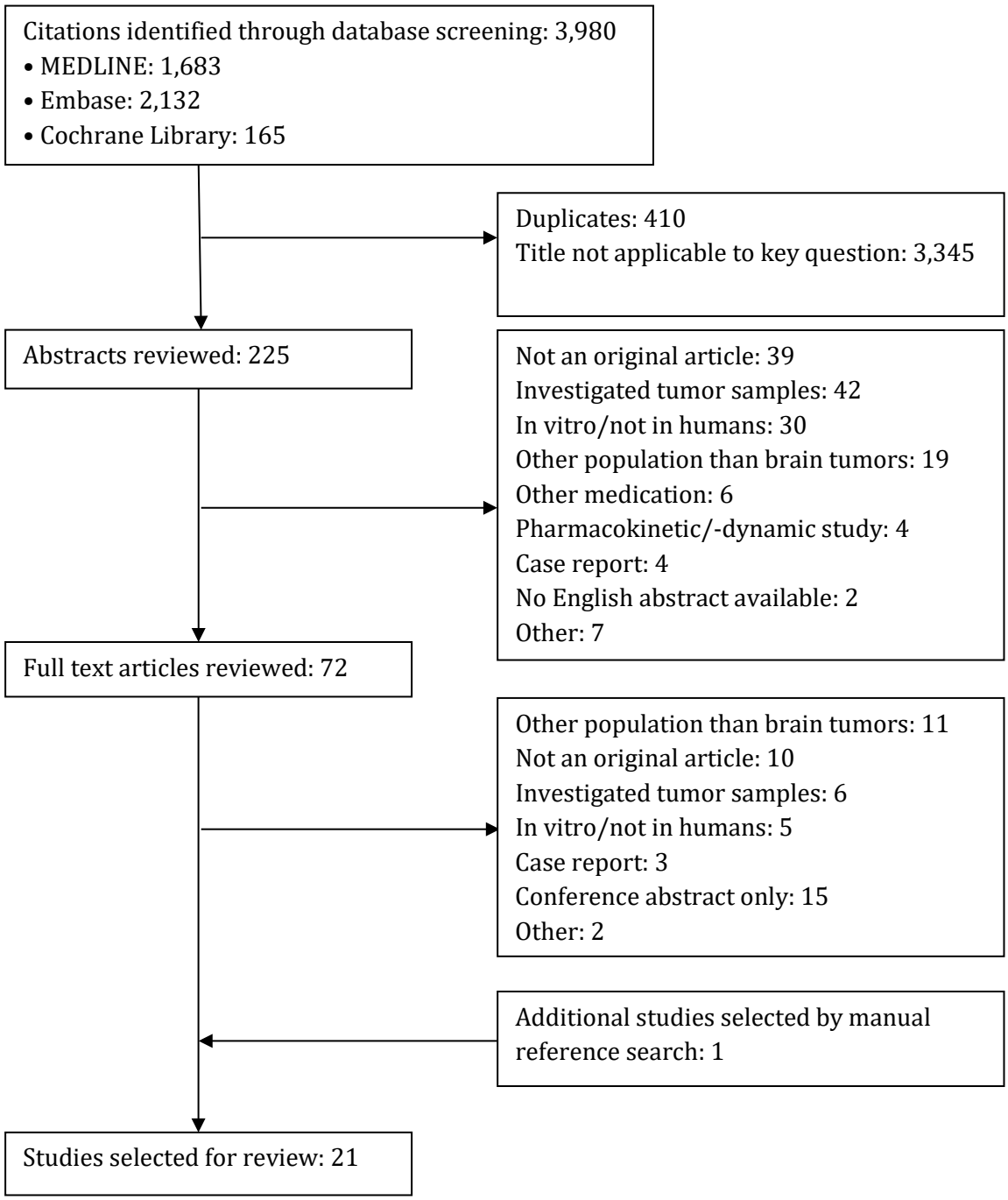

Table 1: Characteristics of studies of treatment efficacy and toxicity in brain tumor patients

First author[Ref]	Year	Study approach	No. of MB/ LGG patients	MB/ LGG	Ethnic origin; nationality	Gene(s) investigated	Outcome measures	Associated variant(s)	(Possible) functional role of the genetic variant
Okcu[27]	2004	Candidate gene approach	n = 44 (of 278)	LGG	Non-Hispanic white; American	*GSTM1* *GSTT1* *GSTP1*	OS, toxicities	None	NA
Barahmani[28]	2008	Candidate gene approach	n = 42	MB	Hispanic, non-Hispanic white, African American, unspecified; American	*GSTM1* *GSTT1*	PFS, toxicities, intellectual impairment	*GSTT1 null* *GSTM1 null*	Enzyme activity ↓
Rednam[29]	2013	Candidate gene approach	n = 89 (of 106)	MB	Non-Hispanic white, Hispanic, other; American	*GSTP1*	PFS, OS, toxicities	*GSTP1* 105 A>G	Enzyme activity ↓
Jin[64]	2016	Candidate gene approach	n = 147 (of 269)	LGG	NS; Chinese	*IL4* *IL13* *IL10* *IL4R*	PFS, OS	*IL4R* r1801275	Unkown

Correa[65]	2016	Candidate gene approach	n = 35 (of 150)	LGG	Caucasian, other; American	*COMT* *BDNF* *DTNBP1*	Neuropsychogical test of attention, executive functions and memory	*COMT* rs4680 *COMT* rs16815 *COMT* rs4646316 *COMT* rs9332377 *COMT* rs4646312 *COMT* rs5993883 *COMT* rs4818 *COMT* rs5746847 *COMT* rs6269 *BDNF* rs11030104 *BDNF* rs10767664 *BDNF* rs10835210 *BDNF* rs2030324 *DTNBP1* rs742106	Dopamine availability ↓ Neural repair ↓ Modulation of neurotransmitter systems

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; OS, overall survival; PFS, progression-free survival; NA, not applicable; NS, not specified.

Table 2: Characteristics of studies of cisplatin-induced ototoxicity in patients with brain tumors

First author [Ref]	Year	Study approach	No. of MB/ LGG patients	MB/ LGG	Ethnic origin; nationality	Gene(s) investigated	Associated variant(s)	(Possible) functional role of the genetic variant
Peters[30]	2000	Candidate gene approach	n = 3 (of 39)[a]	MB	NS; German	*GSTM1* *GSTM3* *GSTT1* *GSTP1* *GSTZ1*	*GSTM3*B*	Enzyme activity ↑
Peters[31]	2003	Candidate gene approach	n = 3 (of 39)[a]	MB	NS; German	Mutations in mtDNA	None	NA
Knoll[32]	2006	Candidate gene approach	n = 7 (of 11)	NS	NS; NS	*GJB2* *SLC26A4* *MTRNR1* *MTTL1* *MTTS1*	None	NA
Riedemann[33]	2007	Candidate gene approach	n = 5 (of 50)	MB	NS; German	*LRP2*	*LRP2* rs2075252	Unknown
Ross[35]	2009	Pathway approach	n = 33 (of 162)	MB/LGG	European, Indian, East Asian; Canadian	220 drug metabolism genes	*TPMT* rs12201199 *COMT rs9332377*	Unknown
Choeyprasert[34]	2012	Candidate gene approach	n = 9 (of 68)	MB/LGG	NS; Thai	*GSTT1* *GSTM1* *LRP2*	*GSTT1*1* *LRP2* rs2228171	Enzyme activity ↓ Unknown

Yang[40]	2013	Candidate gene approach	n = 213	MB	NS; American	*TPMT* *COMT*	None	NA
Pussegoda[39]	2013	Candidate gene approach	n = 70 (of 317)	NS	Caucasian, other; Canadian	*TPMT* *COMT* *ABCC3* *MTHFR* *VKORC1* *SLCO1A2*	*TPMT* rs12201199 *ABCC3 rs*1051640	Unknown Unknown
Lanvers-Kaminsky[42]	2014	Candidate gene approach	n = 12 (of 63)	NS	NS; German	*TPMT* *COMT*	None	NA
Lanvers-Kaminsky[37]	2015	Candidate gene approach	n = 12 (of 64)	NS	NS; German	*SLC22A2* *SLC31A1*	*SLC22A* rs316019	Substrate affinity
Xu[41]	2015	Genome-wide approach	n = 203 (of 238)	MB	NS; American	1,716,999 variants	*ACYP2* rs1872328	Unknown
Brown[38]	2015	Candidate gene approach	n = 71	MB	Non-Hispanic white, Hispanic, other; American	*SOD2*	*SOD2* rs4880	↑ Oxidative stress in cochlea
Olgun[36]	2016	Candidate gene approach	n = 6 (of 72)	MB	NS; Turkey	*ERCC1* *GSTP1* *LRP2* *TPMT* *COMT*	None	None

[a] Studies by Peters *et al*.; same cohorts

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; NA, not applicable; NS, not specified.

Table 3: Characteristics of studies of vincristine-induced neurotoxicity in patients with brain tumors

First author [Ref]	Year	Study approach	No. of MB/ LGG patients	MB/ LGG	Ethnic origin; nationality	Gene(s) investigated	Outcome measures	Associated variant(s)	(Possible) functional role of the genetic variant
Guilhaumou[43]	2011	Candidate gene approach	n = 4 (of 26)[b]	MB/LGG	NS; France	*ABCB1* *CYP3A4* *CYP3A5*	PK parameters	None	NA
Guilhaumou[44]	2011	Candidate gene approach	n = 4 (of 26)[b]	MB/LGG	NS; France	*ABCB1* *CYP3A4* *CYP3A5*	Neurotoxicity events	None	NA
Moore[45]	2011	Candidate gene approach	n = 7 (of 50)	NS	Caucasian, Hispanic, Asian, Pacific Islander, Australian Aboriginal; Australian	*CYP3A5*	Neurotoxicity	None	NA

[b] Studies by Guilhaumou *et al.*; same cohorts

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; NA, not applicable; NS, not specified; PK, pharmacokinetics.

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ABBREVIATIONS

ABC	ATP-binding cassette
ACYP	Acylphosphatase
ALL	Acute lymphoblastic leukemia
COMT	Catechol-O-methyltransferase
CYP	Cytochrome P450
DPYD	Dihydropyrimidine dehydrogenase
GST	Glutathione S-transferase
GWAS	Genome-wide association study
IL	Interleukin
LGG	Low-grade glioma
LPR	Low-density lipoprotein (Megalin)
MB	Medulloblastoma
NS	Not specified
OR	Odds ratio
OS	Overall survival
PK	Pharmacokinetics
PNET	Primitive neuro-ectodermal tumor
SNP	Single-nucleotide polymorphism
SLC	Solute carrier
SOD	Superoxide dismutase
TPMT	Thiopurine S-methyltransferase

SUPPLEMENTARY

Supplementary table 1: Search strategy for electronic databases

Electronic databases searched	MEDLINE, Embase, Cochrane Library
General search strategy	Keywords and, when available, MeSH-terms were used to draft a search strategy combining the following three elements: "Brain tumor", "Chemotherapy" and "Genetics". Synonyms and related terms were used when appropriate. To broaden the number of articles useful for this systematic review, the first search strategy was combined with a second strategy, consisting the elements "Cisplatin / Carboplatin / Vincristine / Cyclophosphamide / Etoposide / Lomustine", "Genetics" and "Toxicity". By leaving the disease component out of this strategy, studies with heterogeneous cohorts could be identified. These articles were manually screened for presence of brain tumor patients in their cohorts.
Date of search	30th of October, 2016

Search terms used*:

(((("Brain Neoplasms"[Mesh] OR "Medulloblastoma"[Mesh] OR "Glioma"[Mesh] OR "Astrocytoma"[Mesh] OR "Optic Nerve Glioma"[Mesh] OR "Oligodendroglioma"[Mesh] OR "Ganglioglioma"[Mesh] OR brain neoplasm*[Title/Abstract] OR brain cancer[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain tumour*[Title/Abstract] OR medulloblastoma[Title/Abstract] OR glioma[Title/Abstract] OR astrocytoma[Title/Abstract] OR oligodendroglioma[Title/Abstract] OR ganglioglioma[Title/Abstract]) AND ("Drug Therapy"[Mesh] OR drug therapy[Title/Abstract] OR chemotherapy[Title/Abstract] OR "Vincristine"[Mesh] OR vincristine[Title/Abstract] OR "Cisplatin"[Mesh] OR cisplatin[Title/Abstract] OR "Carboplatin"[Mesh] OR carboplatin[Title/Abstract] OR "Cyclophosphamide"[Mesh] OR cyclophosphamide[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract])) OR (("Cisplatin"[Mesh] OR cisplatin[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR ototoxic*[Title/Abstract] OR hearing loss[Title/Abstract])) OR (("Carboplatin"[Mesh] OR carboplatin[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR ototoxic*[Title/Abstract] OR hearing loss[Title/Abstract])) OR (("Vincristine"[Mesh] OR vincristine[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR

"Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR “Polyneuropathies"[Mesh] OR polyneuropathy[Title/Abstract] OR neuropathy[Title/Abstract] OR neurotoxicity[Title/Abstract])) OR (("Cyclophosphamide"[Mesh] OR cyclophosphamide[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract]OR "Renal Insufficiency"[Mesh] OR "Kidney Failure, Chronic"[Mesh] OR nephrotoxic*[Title/Abstract] OR renal failure[Title/Abstract] OR kidney failure[Title/Abstract])) OR (("Etoposide"[Mesh] OR etoposide[Title]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract])) OR (("Lomustine"[Mesh] OR lomustine[Title]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract])))

* The search terms used in MEDLINE are shown; comparable search terms were used for the other electronic databases.