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REVIEW ARTICLE

Do pharmacokinetic polymorphisms explain treatment failure in high-risk patients with neuroblastoma?

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Abstract
Purpose Neuroblastoma is the most common extracranial solid tumour in childhood. It accounts for 15% of all paediatric oncology deaths. In the last few decades, improvement in treatment outcome for high-risk patients has not occurred, with an overall survival rate <30–40%. Many reasons may account for such a low survival rate. The aim of this review is to evaluate whether pharmacogenetic factors can explain treatment failure in neuroblastoma.
Methods A literature search based on PubMed's database Medical Subject Headings (MeSH) was performed to retrieve all pertinent publications on current treatment options and new classes of drugs under investigation. One hundred and fifty-eight articles wer reviewed, and relevant data were extracted and summarised.
Results and conclusions Few of the large number of polymorphisms identified thus far showed an effect on pharmacokinetics that could be considered clinically relevant. Despite their clinical relevance, none of the single nucleotide polymorphisms (SNPs) investigated can explain treatment failure. These findings seem to reflect the clinical context in which anti-tumour drugs are used, i.e. in combination with multimodal therapy. In addition, many pharmacogenetic studies did not assess (differences in) drug exposure, which could contribute to explaining pharmacogenetic associations. Furthermore, it remains unclear whether the significant activity of new drugs on different neuroblastoma cell lines translates into clinical efficacy, irrespective of resistance or myelocytomatosis viral related oncogene, neuroblastoma derived (MYCN) amplification. Elucidation of the clinical role of pharmacogenetic factors in the treatment of neuroblastoma demands an integrated pharmacokinetic–pharmacodynamic approach to the analysis of treatment response data.

Keywords Neuroblastoma · Pharmacogenetics · Pharmacokinetics · Cytotoxic drugs · Modelling & simulation · PKPD modelling

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Introduction

Neuroblastoma

Neuroblastoma (NB) is the most common extracranial solid tumour in childhood and belongs to the group of "small blue round cells" neoplasms. It accounts for 15% of all paediatric oncology deaths [1–3]. Its incidence peaks at age 0–4 years, and <5% of patients are older than 10 years of age [2]. It is a neuroendocrine tumour tightly connected to the sympathetic nervous system (SNS). Given that it originates from the primitive neuroepithelial cells of the neural crest, it can develop anywhere in the SNS. Fifty percent of primary tumours arise in the adrenal medulla, but other common sites are neck, chest, abdomen, and pelvis. At diagnosis, in most cases, neuroblastoma has already metastasised, usually to liver, bone, bone marrow, lymph

nodes, and skin [1–3]. Despite its prevalence and invasiveness, the aetiology of neuroblastoma is still poorly understood. Few causative factors have been identified: familiar forms are rare (about 1%); there is no clear genetic predisposition, and presumably tumorigenesis may require alterations in more than one gene. The hallmark of the tumour is heterogeneity; its behaviour can vary from a localised tumour, easy to resect with surgery, to a metastatic progressive one, with high resistance and poor outcome; strikingly, in 5% of cases, it manifests a spontaneous regression. Prognosis, in the same manner, ranges from overall survival (OS) to high fatality risk. Because of the tumour heterogeneity, biomarkers have been used to select the appropriate treatment schedule according to a risk-group classification. Myc myelocytomatosis viral related oncogene, neuroblastoma derived (MYCN) amplification, chromosomal loss (1p) or gain (17q), DNA index (near diploid), age >18 months, and International Neuroblastoma Staging System (INSS) stages III and IV, are all predictors of poor prognosis and disease malignancy [1–7]. As with MYCN, many other biomarkers have been studied to define phenotype (disease severity) and stratify patients, such as e.g. the tyrosine kinase (Trk) family of neurotrophin receptors, which are important regulators of survival, growth, and differentiation of normal neuronal cells; high expression of TrkB and TrkA III is associated with MYCN amplification and poor outcome, whereas high expression of TrkA is associated with a favourable status. In spite of these data, to date only the amplification of the oncogene MYCN can be considered as an independent marker of tumour status and treatment outcome [1, 2]. The current risk-group classification of the disease and the corresponding treatment protocols have therefore been defined according to tumour behaviour and biomarker prediction.

Although in the last 20 years this approach substantially improved treatment outcome for low- and intermediate-risk patients, to date, there has been little improvement in the high-risk patient group. Despite intensive polytherapy, high-risk patients still only have an OS rate of 30–40% [1, 3]. There may be several reasons for the low OS rate. Considering that important associations have been demonstrated between pharmacogenetics and efficacy in different solid tumours (e.g., increased efficacy of Herceptin in the treatment of human epidermal growth factor receptor 2 (HER-2)-positive breast cancers with benefits in terms of disease-free (DFS) and OS [8–10]), the aim of this review was to explore the role of pharmacogenetics in the treatment of neuroblastoma. The main question to be addressed is whether pharmacogenetic differences can (partly) explain treatment failure. In addition, we propose the use of model-based interventions, such as different dosing algorithms, to improve the outcome of therapy and the safety profile of current and novel drugs in high-risk patients.

Pharmacogenetics

In the context of our review, the term pharmacogenetics is considered as defined by the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), even if other definitions have been reported in the scientific literature. According to the proposed ICH definitions, pharmacogenomics is the investigation of variations of DNA and RNA characteristics as related to drug response. Pharmacogenetics is a subset of pharmacogenomics and is defined as the influence of variations in DNA sequence on drug response [8]. Pharmacogenetics is a relatively new field of research, which aims to improve medical knowledge using DNA sequence information [11, 12].

Clinical research on prognostic, risk and covariate factors often assigns a privileged position to pharmacogenetics compared with other determinants of drug response. This approach often disregards the multivariate nature of the interaction between all relevant factors underlying treatment response, which may cause biased analysis and misinterpretation of the findings. Too narrow a vision of the clinical factors contributing to variability reduces the opportunity to understand the true role of pharmacogenetics and to relate it to real-life applications. It is critical to realise that pharmacogenetics is only one of the many factors that can influence pharmacokinetics, pharmacodynamics and clinical response, and that these factors can interact with each other. This review represents an effort to answer the questions posed above 1) by evaluating the role of pharmacogenetics on the pharmacokinetics of cytotoxic drugs used in the treatment of neuroblastoma and 2) by highlighting the requirements to evaluate its role in new therapeutic interventions. In addition, suggestions are given for alternative therapeutic approaches, which can potentially reduce treatment failure.

Methods

Literature search on PubMed's database Medical Subject Headings (MeSH) was performed to retrieve relevant published data. The search method involved structured keywords and was divided into two phases.

In the first phase, attention was given to cytotoxic drugs currently used for the treatment of neuroblastoma. In the first step, the drug's generic name was associated to four general keywords: pharmacokinetics, pharmacogenetics, neuroblastoma, and leukaemia. Subsequently, the drug name was associated to specific elements of drug disposition. In the secon phase, new classes of drugs currently in clinical development were evaluated. The search involved retrieval of all publications related to the treatment of neuroblastoma, which focused on pharmacogenetics. In

addition, pharmacokinetic data on the aforementioned drugs were retrieved from paediatric studies, and especially from studies of patients affected by neuroblastoma or leukaemia [13–59]. Conversely, pharmacogenetic data were gathered from any available study [60–123]. We decided to exclude references related to genetic variations in pharmacodynamics and disease.

A total of 158 articles and reviews were used for abstraction and extraction. Data on exposure, efficacy and toxicity were summarised using MS Excel spreadsheets. An overview of the findings and potential relevance of genetic variation is presented for both cytotoxic drugs (Tables 1, 2, and 3) and drugs under clinical investigation (Tables 4, 5, and 6).

Results

Cytotoxic drugs

The use of cytotoxic drugs in neuroblastoma treatment is considered as an adjuvant or add-on therapy to chemotherapy (CT), radiotherapy, surgical resection, stem-cell transplantation, and treatment of minimal residual disease (MRD) [3]. CT approaches used in low-, intermediate-, and high-risk patient groups present differences in terms of dosing regimens and drug associations. In high-risk patients, cytotoxic drugs are used in two different phases of treatment: first, during induction CT, which is aimed at metastasis control and primary tumour resection; and second, during myeloablative chemotherapy (or high-dose CT) in association with stem-cell transplantation with the aim of consolidating induction CT and surgery [3]. Despite the various treatment approaches, high-risk groups have a very low OS rate (30–40%) [1, 3]. To clarify whether or not genetic variants could explain the lack of response, the role of pharmacogenetics in influencing pharmacokinetics of six of the main cytotoxic drugs used in neuroblastoma treatment was evaluated. Without taking into account the nature of treatment as adjuvant therapy, it was found that only few single nucleotide polymorphisms (SNPs) show a relevant effect on pharmacokinetics. In agreement with our hypothesis, published results seem to confirm that an SNP must affect a key enzyme or pathway to translate genetic variation into clinically relevant differences. Tables 1, 2 and 3 provide the summary of the findings. The most relevant polymorphisms evaluated are briefly described in the following paragraphs.

Irinotecan

To date UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1)*28 is the only SNP introduced in a label (US) among all cytotoxic drugs included in this review. It is noteworthy to emphasise that UGT1A is the main enzyme in controlling deactivation of 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan. The label of CAMPTOSAR (irinotecan hydrochloride injection) has been revised with the following pharmacogenetic information: patients homozygous for the UGT1A1*28, who undergo a single-agent treatment with irinotecan, have a higher exposure to the active metabolite and are at increased risk for neutropenia [8]. In fact, various publications seem to confirm higher exposure to SN-38 [85, 89, 90, 107–109, 115, 116, 119] and the increased risk for neutropenia [85, 100, 108, 113, 115, 117] in patients harbouring the UGT1A1*28 allele. On the same enzyme, another SNP showed a similar effect on SN-38 exposure. Studies on the UGT1A1*6, SNP expressed in Asian individuals also showed higher exposure to the active metabolite [86, 88, 89, 106, 110] and an increased risk for neutropenia [86, 88, 89]. However, further studies are needed to assess the clinical value of UGT1A1*6.

Vincristine

According to Dennison et al. [60, 69], and Renbarger et al. [68], cytochrome P450 (CYP)3A4 and CYP3A5 play key roles in metabolising vincristine to its main metabolite (the secondary amine M1), with a 9- to 14-fold higher selectivity for CYP3A5. As mentioned earlier, polymorphisms affecting the primary metabolic pathway are required to influence the pharmacokinetic profile of a drug. Although in the study by Dennison et al. patients with a high expression of CYP3A5 (homozygous: *1/*1; heterozygous: *1/*3, *1/*6) showed lower exposure to vincristine, and patients with a low expression of the enzyme (homozygous: *3/*3; heterozygous: *1/*7) showed increased exposure, further studies are needed to confirm the hypothesis that SNPs in CYP3A5 do contribute to the interindividual variability in vincristine metabolism.

Other cytotoxic drugs

No SNPs analysed thus far appeared to affect the pharmacokinetic profile of cisplatin, melphalan, etoposide or doxorubicin in a way that can be considered clinically relevant.

Drugs in clinical development

To significantly improve the treatment of neuroblastoma, several studies were carried out to evaluate the potential of novel therapeutic alternatives. New approaches to circumvent the high resistance of neuroblastoma cells to chemotherapy

could have a great impact on future treatment options. Seven new classes of drugs were identified that may contribute to that objective. Mechanisms of action, metabolic pathway and efficacy on neuroblastoma cells were assessed, with particular attention being paid to pharmacogenetic effects. Tables 4, 5, and 6 provide a summary of the findings from published pharmacogenetic studies.

17-N-allylamino 17-demethoxygeldanamycin (17-AAG)

Heat-shock protein 90 (Hsp90), an essential chaperone involved in the conformational maturation and stability of different proteins, including regulators of cellular proliferation and inhibitors of apoptosis, is constitutively overexpressed in tumour cell lines [124]. The great advantage of Hsp90 inhibitors should be the simultaneous depletion of multiple oncogenic client proteins [125]. Kang et al. [124] demonstrated the inhibition of SK-N-SH and LAN-1 neuroblastoma cell-line growth by 17-AAG, accompanied by reduced levels of Raf-1 and Akt protein kinases. On the other hand, Jayanthan et al. [125] showed that all neuroblastoma cell lines under evaluation (SK-N-MC, SK-N-SH, SK-N-BE2, IMR32, SH-Sy5y, LAN1, SHEP, IMR-5 and NUB-7) were sensitive to 17-AAG, with a half maximal inhibitory concentration (IC_{50}) value ranging from 0.5 to 5 μM across different cell lines. In the same study, 17-AAG also sensitised neuroblastoma cells to various chemotherapeutic agents. 17-AAG is metabolised by CYP3A4 and CYP3A5 to the active metabolite 17-AG and by nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) dehydrogenase quinone 1 (NQO1) to the very active metabolite 17-AAGH2. The SNP NQO1*2, which seems to deplete enzyme activity, induces a 32-fold increase in 17-AAG resistance [96, 97], suggesting that such variation could have a relevant effect on the clinical response. Further studies are needed to characterise the role of NQO1 and other related polymorphisms in 17-AAG metabolism. In addition, it should be noted that polymorphisms affecting CYP450 are unlikely to influence the pharmacodynamics of 17-AAG because the metabolite has a similar activity to the parent compound.

Aprepitant

In addition to its role in the regulation of neurogenic inflammation, pain and depression, the activation of the neurokinin 1 (NK1) receptor by substance P induces mitogenesis and regulates active migration of tumour cells and angiogenetic processes. Aprepitant, a specific inhibitor of NK1, can inhibit both DNA synthesis and cell proliferation through the mitogen-activated protein kinase (MAPK) pathway [126]. In the study by Muñoz et al. [126], aprepitant showed a cytotoxic activity on all tested glioma, neuroblastoma, retinoblastoma, pancreatic carcinoma, larynx carcinoma, gastric carcinoma and colon carcinoma cell lines. Furthermore, after its administration, a great number of apoptotic cells were found in all tumour cell lines. Aprepitant is metabolised mainly by CYP3A4, with CYP1A2 and 2C19 as secondary metabolic routes. Thus far, as reported in Table 2, data on pharmacogenetic variation has not been reported.

BMS-536924

Through the IGF-1 receptor, insulin-like growth factor regulates many cellular survival mechanisms, such as cellular growth, differentiation, apoptosis, tumour angiogenesis and metastasis, and different tumour types have shown overexpression of this receptor [127]. All neuroblastoma cell lines tested in the study by Huang et al. [127] were sensitive to treatment with BMS-536924 (IC_{50} range: 0.136-0.277 μmol/L), a specific inhibitor of IGF-1R, but the treatment seems to be successful only when the receptor is on the critical path of the pathogenesis and tumour progression. The same study demonstrated an interaction between BMS-536924 and gefitinib [epidermal growth factor receptor (EGFR) inhibitor] or BMS-690514 (panHER inhibitor). Such evidence raises an important issue regarding the mechanisms of resistance by single agents, which involves the adaptation to an IGF-independent growth mechanism. No pharmacogenetic data have been published on this drug.

Eflornithine (alpha-difluoromethylornithine)

Polyamines, essential molecules for cellular activity, are undoubtedly involved in tumour cell growth [128]. If their synthesis is inhibited, cell growth is stopped or severely retarded. One of the hallmarks of neuroblastoma MYCN-amplified cell lines is the polyamine expansion [129]. Ornithine decarboxylase (ODC1) is a key enzyme in the biosynthetic pathway of polyamines, and ODC1 at high levels correlates with poor outcome in neuroblastoma. Eflornithine [d,l-α-difluoromethylornithine (DFMO)] has been shown to induce cell-cycle arrest (G1) inhibiting ODC1 in neuroblastoma cell lines. The underlying cause is a polyamine depletion that arrests the cell cycle through the cyclin-dependent kinase inhibitor (p27kip1) pathway. Wallick et al. [128] demonstrated its inhibitory activity on neuroblastoma cell lines LAN-1 and NMB-7, with a near-total cessation of cellular growth after 3 days. Whereas Koomoa et al. [130] confirmed the inhibition of LAN-1 proliferation, in another study by Rounbehler et al. [131], DFMO preferentially abolished the growth of MYCN-amplified cell lines. DFMO also increased the effects of chemotherapy without additional toxicity [129]. It is important to point out that the polyamine depletion, besides cell-cycle arrest, also induces a mechanism of cell

survival through the PI3K/Akt pathway that could explain a possible moderate efficacy of DFMO alone. Given that eflornithine is not metabolised, pharmacogenetic information pertinent to drug disposition is not available.

Imatinib mesylate

The 2-phenylaminopyrimidine imatinib is a specific inhibitor of Trk enzymes. It binds the Trk domain of Abl, c-kit (or CD117), and platelet-derived growth factor receptor (PDGF-R). C-Kit and PDGF-R were detected in neuroblastoma [132–134], and the cytokine receptor seems to be expressed mainly in the most aggressive forms of the tumour [135]. PDGF plays an important role in controlling growth, differentiation and survival of glial cells and immature neuroblasts, whereas c-Kit is essential for normal haematopoiesis, gametogenesis and melanogenesis [134]. *In vitro* studies by Vitali et al., Beppu et al., Rossler et al., and Palmberg et al. [132–135] demonstrated the ability of imatinib to inhibit neuroblastoma proliferation. Imatinib is metabolised by a large number of enzymes of the CYP450 family, with a major role played by CYP3A4 and CYP3A5. It is also a substrate of the ATP-binding cassette (ABC) transporters, P-glycoprotein (Pgp) and ABCG2. The most common polymorphisms associated with these routes only have a limited influence on imatinib pharmacokinetics and therefore do not seem to be the underlying cause of the high interindividual variability observed in clinical data [98, 136].

Nutlin-3

Murine double minute (MDM2) is a negative regulator of p53. It prevents p53 control on cell cycle and apoptosis, inhibiting transcriptional activation of the tumour suppressor. However, the effectiveness of an MDM2 inhibitor is evident only if p53 is functional. Given this prerequisite, it is important to emphasise that <2% of neuroblastoma tumours exhibit mutations on the *TP53* gene [137]. Nutlin-3 is a specific chiral inhibitor of MDM2, which induces G1 cell-cycle arrest, apoptosis and neuronal differentiation in neuroblastoma cells [137–140], with an IC_{50} value of 3.25 μmol/L [141]. The 3a enantiomer shows a ~200-fold higher affinity for MDM2 than the enantiomer 3b [141]. Nutlin-3 is also a Pgp substrate, and both enantiomers increase the cytotoxic activity of anticancer agents that are substrates of Pgp (e.g., Vincristine) [140]. No pharmacogenetic information is available for this compound.

Oncolytic virus

Oncolytic viruses represent a new important therapeutic approach in cancer treatment [142–145]. They can circumvent chemotherapy-induced resistance mechanisms through a specific lysis of tumour cells. In addition, evidence exists of their efficacy and safety in clinical trials [146–148]. They basically act by inducing cell lysis, and genetic mutations applied to their genome restrict viral replication only to the tumour cells. An interesting feature of these viruses is the opportunity to incorporate an additional mechanism of action by arming the virus against specific targets (examples are listed below).

Neuroblastoma cells show evidence of cancer stem cells, as confirmed by the expression of various stem-cell markers such as CD34, CD133, and nestin. These cells can form tumorspheres extremely resistant to chemotherapy treatment and cause tumour relapse [146]. Given that neuroblastoma is also highly susceptible to herpes simplex virus (HSV)-mediated oncolysis [147, 149, 150], the use of HSV represents the best solution for a possible application in neuroblastoma treatment.

On the other hand, nestin, a protein expressed in nerve cells and involved in radial growth of the axon, is one of the possible options with which to arm an oncolytic virus. Thomas et al. [151] and Mahller et al. [146] demonstrated a correlation between nestin expression and MYCN amplification, although the same correlation was not shown in the study by Korja et al. [152]. In the former study, rQNestin34.5 oHSV abolished tumour formation for >60 days in mice affected by neuroblastoma [146].

Other possible options, besides the nestin-targeted vector, is the use of HSV armed with immunomodulatory molecules [B7-1, interleukin (IL)-12 and IL-18], armed against activated Rat sacroma (Ras)-signalling pathway, or with inhibitors of the matrix metalloproteinases (TIMP-3), as demonstrated respectively by Ino et al., Li et al. and Mahller et al. [147, 148, 150]. No pharmacogenetic data have been found for this type of intervention.

Discussions and conclusion

To date, limited improvement in survival rates has been achieved for high-risk patients with neuroblatoma. In this review, we have explored whether pharmacogenetic variation in pharmacokinetics could explain treatment failure. In addition, we have attempted to highlight some of the research gaps in the evaluation of novel molecules for neuroblastoma treatment. Numerous pharmacogenetic studies have been performed during the last 10 years, but most of them are basically related to drug disposition, rather than to pharmacodynamics. Based on the published literature, pharmacokinetic polymporphisms do not seem to be the cause of the low survival rate in neuroblastoma. None of the SNPs analysed thus far can explain the poor prognosis in high-risk patients following a variety of treatment options. The lack of correlation between response and pharmacogenetic factors may also reflect

the context in which drugs are used (i.e. response is the result of a multimodal approach to neuroblastoma). Furthermore, it can be inferred from the low therapeutic failure in low- and intermediate-risk patients that the presence of pharmacokinetic polymorphisms in those groups does not alter treatment response rate. Assuming that systemic pharmacokinetics is independent of disease severity, it is conceivable that tumour factors associated with tissue kinetics (e.g. changes in Pgp expression) could lead to relevant differences in tumour exposure. Even though such differences at tissue level cannot be captured by the analysis of blood or plasma data, pharmacodynamic variants may ultimately underlie differences in response rates.

From the available data, only a few of the large number of polymorphisms have a clinically relevant effect on pharmacokinetics. Among these, SNPs UGT1A1*28 (already part of the label of CAMPTOSAR in the USA) and UGT1A1*6 were shown to affect the pharmacokinetic profile of irinotecan. Both polymorphisms cause an increase in the exposure to the active metabolite SN-38 and consequently the risk for neutropenia. Moreover, it was shown that polymorphisms affecting the CYP3A5 can alter the pharmacokinetics of vincristine, given that this isozyme plays a key role in vincristine elimination. The same can be assumed from the investigation by Kelland et al. and Guo et al. on NQO1. This enzyme metabolises 17-AAG to the active metabolite 17-AAGH2; and the polymorphic variant NQO1*2, which causes deletion of enzymatic activity, increases treatment resistance by 32-fold.

From the examples above, it is clear that genetic variation in drug metabolism is not always clinically relevant per se. Its relevance depends on the enzyme affected, its impact on the metabolic capacity and especially on the contribution of the pathway to the overall clearance of a given drug. The same concept is applicable to the role of pharmacogenetics on active transporters and their implications for drug disposition. Taking these considerations into account, one needs to characterise a drug's overall pharmacokinetic profile to evaluate and demonstrate the potential consequences of genetic polymorphisms. Given that compensatory pathways are involved in the disposition of the majority of drugs suitable for clinical use, it can be anticipated that pharmacogenetic variation in absorption, distribution, metabolism, and excretion (ADME) will often have limited impact on the variability observed in pharmacodynamics and response. On the other hand, pharmacogenetic variation should not be overlooked if single pathways are known to determine drug disposition. This is one of the reasons so few drug labels yield useful pharmacogenetic information. In fact, numerous other intrinsic and extrinsic factors can influence pharmacokinetics, including variation in dosing regimen, treatment compliance, drug–drug interactions, demographic covariates, disease and organ function. For instance, in the specific case of neuroblastoma, most patients are aged between 0 and 4–5 years, and the large variability in exposure could exclusively be assigned to developmental growth (i.e. ontogeny) rather than genetic variation. Furthermore, other important elements such as organ function (i.e. disease severity) and drug–drug interactions are likely to have equal or higher impact than pharmacogenetic factors on drug disposition.

In brief, the scenario arising from this review confirms the need for an integrated approach to the evaluation of genetic variation in ADME processes. Inferences about the clinical implications of a polymorphism depend upon an integrated assessment of the exposure–response relationship. With regard to drugs under clinical investigation, our review has identified compounds with prominent pharmacological activity on neuroblastoma cells, irrespective of the level of resistance and MYCN amplification. Amongst them, oncolytic viruses have raised great interest due to the evidence of a cancer stem cell, which may underlie the high resistance to chemotherapy. Oncolytic treatment, circumventing the traditional mechanism of resistance, seems to be a valuable solution to improve treatment outcome. At this time, however, it is difficult to state whether such activity translates into clinical efficacy. Further studies are needed to confirm the clinical value of novel classes of drugs in neuroblastoma treatment. Moreover, effective drug combinations and dosing algorithms still need to be identified to ensure maximum effectiveness for most compounds.

Going back to the role of pharmacogenetics, this review shows the importance of the context in which a drug is used for the evaluation of polymorphisms. Many intrinsic and extrinsic factors influence pharmacokinetics, pharmacodynamics and overall response to treatment. Therefore, an isolated analysis of the role of pharmacogenetic factors on ADME processes would probably lead to biased results. All other relevant covariates should be considered in the statistical analysis of pharmacogenetic data. In this sense, many pharmacogenetic studies summarised in this review have not considered such an integrated approach or included details about the primary pharmacokinetic parameters.

In conclusion, pharmacogenetics is only one of many factors associated with pharmacokinetic variability. A model-based approach is required to address questions regarding the impact of polymorphism on clinical response and, as such, should become best practice in the analysis of pharmacogenetic data [153–157]. In a model-based approach, data analysis comprises the use of mathematical and statistical concepts that describe longitudinal data (i.e. a disease model), exposure–response relationships (i.e. a drug model) and clinical trial design features (i.e., an implementation model) in an intergrated manner. The main advantage of this approach is that all relevant covariates (such as age,

weight, ethnicity, etc.) can be taken into account concurrently. Furthermore, between- and within-subject variability is assessed parametrically in terms of physiological parameters, such as clearance and volume of distribution, rather than relying on the observed variables (e.g. peak concentration, C_{max}), which are often prone to experimental artefacts. In this sense, modelling represents an effective strategy for translating the clinical implications of pharmacogenetic variation. Most importantly, it can support the selection and individualisation of dosing regimens, which may be more critical for efficacy than the effects of ADME polymorphism in high-risk patients with neuroblastoma.

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Appendix

Table 1 Influence of pharmacogenetics on the pharmacokinetic profile of cytotoxic drugs

	EXPOSURE					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
CYP1A2					**NK**	
CYP2C19		**NK**				
CYP2D6		**NK**				
CYP2E1					**NK**	
CYP3A4	**NA** *1B: –392 A > G [115, 116, 124]	**NK**			⬆3A4 A/A[77]	**NK**
	NA *2: 15713T > C [116]					
	NA *3: 23172T > C [115, 116, 121]					
	NA *4: 352A > G [124]					
	NA *5: 653C > G [124]					
	NA *6: 831 insA [124]					
	NA *17: 15615T > C [116, 121]					
	NA *18: 20070T > C [116, 121]					
	NA *1G, *16B, *18B [93]					
CYP3A5	**NA** *3C: 22893G > A [115, 116, 121, 124]	⬇3A5*1/*1[61,69,70]			⬆3A5 G/G[77]	
	NA *6: 30597G > A [115, 116, 124]	⬇3A5*1/*3[61,69,70]			⬆3A5 A/A[77]	
	NA 6986 A>G [88]	⬇3A5*1/*6[61,69,70]				
		⬆3A5*3/*3[61,69,70]				
		⬆3A5*1/*7[61,69,70]				
GST			**NK**	**NK**	⬆P1 A/A[77]	**NA** GSTM1 null[85]
						NA GSTT1 null [85]
UGT	**NA** 1A1*6: 211G > A [101, 102, 109, 118]				⬆1A1 7/7[77]	
	⬆(SN-38) 1A1*6: 211G > A[107, 111]					
	⬆(SN-38) 1A1*6 G/G[87, 89]					
	⬆(SN-38) haplotype with 1A1*6[90]					
	NA 1A1*7: 1456T > G [115, 118]					
	⬆(SN-38) 1A1*7: 1456T > G[107, 111]					
	NA 1A1*27: 686C > A [109]					
	⬆(SN-38) 1A1*27: 686C > A[107, 111]					
	NA 1A1*28: (TA)7TAA[88, 89, 94, 101,103,106,114,118,121,124]					
	⬆(SN-38) 1A1*28: (TA)7TAA[86,90,91,108,109,110,116,117]					
	⬆(SN-38) 1A1: haplotype*6, haplotype*28[120]					
	⬆(SN-38) 1A1*35: 1291T > C[107]					
	NA 1A1*36: (TA)5TAA [121]					
	NA 1A1*37: (TA)8TAA [103]					
	NA 1A1: –3156G>A [88, 109]					
	⬆(SN-38) 1A1: 686C > T[113]					
	NA 1A6*2: 19T > G, 541A > G, 552A > C [103]					
	NA 1A7*2: 387T > G, 391C > A, 392G > A [102]					
	NA 1A7*2: 387T > G, 391C > A [103]					
	NA 1A7*3: 387T>G,391C>A,392G>A,622T>C [102]					
	NA 1A7*3: 387T > G, 391C > A, 622T > C [103]					
	NA 1A7*4: 622T > C [102]					
	NA 1A7:33C>A,343G>A,387T>G,391C>A, 392G>A,417G>C,582T>C [86]					

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate that the gene is not related to the pharmacokinetics of the drug.

Table 1 (continued)

	EXPOSURE					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
UGT	**NA** 1A7*2: 387T > G, 391C > A [107]					
	NA 1A7*2: 387T > G, 391C > A [122]					
	⬆(SN-38) 1A7*3: 387T>G,391C>A,622T>C[107]					
	⬆(SN-38) 1A7*3: 387T>G,391C>A,622T>C[122]					
	⬆(SN-38) 1A7*4: 622T > C[107]					
	⬆(SN-38) 1A7*4: 622T > C[122]					
	⬆(SN-38) 1A7*5: (G115S)[122]					
	NA 1A7*6: (E139D) [122]					
	NA 1A7*7: 387T > G, 391C > A, (E139D) [122]					
	⬆(SN-38) 1A7*8: 387T>G, 391C>A,(E139D),622T>C[122]					
	⬆(SN-38) 1A7*9: (G115S),387T>G,391C>A[122]					
	NA 1A9*2 [86]					
	NA 1A9*3: 98T > C [117]					
	NA 1A9*3: 98T > C [86]					
	NA 1A9*5: 766G > A [117]					
	NA 1A9–118 (dT)9/9 [103]					
	NA Haplotype: UGT1A1*1, UGT1A6*1, UGT1A7*1,UGT1A9–118 (dT)10/10 [103]					
	NA 1A9*2: 8G > A [122]					
	⬆(SN-38) 1A9*3: 98T > C[122]					
	⬆(SN-38) 1A9*5: 766G > A[112]					
CBR1						**NA** c.219 G>C [79]
						⬇ c.627 C/C[79]
						⬇ +967 G/G[79]
						⬇ diplotype (c.627C,+967G)[79]
						⬇ 1096 G/G[80]
						⬆ V88I[82]
						NA P131S [82]
CBR3						**NA**[79]
CES1	**NA** 1440 A>T [115]					
	NA 1525 A>C [115]					
CES2	**NA** 1647 C>T [115]					
	NA *1: 803C>G,8721G>A,9938G>A,9943C>A [104]					
	NA *2: 8721G > A [104]					
	NA *3: 8721G > A, 9607C > T, 9624A > G, 9938G > A, 9943C > A [104]					
	NA *4: 8721G > A, 9938G > A, 9943C > A [104]					
	NA *7: 4595T > C [104]					
	NA *8: 7339G > A [104]					
	NA *10: 1216T > C, 9938G > A, 9943C > A [104]					
	NA Haplotype 50-UTR-363, Intron1 + 1361 [123]					
	NA Haplotype 50-UTR-363, Intron1 + 947, Intron1 + 1361, Intron1 + 1643 [123]					

Table 1 (continued)

	EXPOSURE					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
VDR					⬆intron 8AA/AG[77]	
					⬆fok 1TT[77]	
MDR1		**NA** C3435T [62]	**NK**		**NK** G571A [72]	**NA** G571A [72]
		NA G2677T [62]			⬇3435 C/C[77]	**NK** G1199A [83]
		NK G1199A [71, 83]			**NK** 3435 C/C [78]	**NA** G1199A [71]
		NK G571A [72]			⬇2677 G/G[77]	**NK** G1199T [83]
		NK G1199T [83]			**NA** G2677T [78]	
					NK Haplotype 2677G-3435C [78]	
MRP1			**NK**			**NK** Gly671Val G/T, T/T [81]
MRP2			**NK**			**NK** haplotype Val1188Glu-Cys1515Tyr [81]
ABCB1(MDR1)	⬆(SN-38) Haplotype: 1236C > T, 2677G > T, and 3435C > T[119]	**NA** 893-Ser [63]				
	⬆(SN-38) 1236C > T[115]	**NA** 893-Thr [63]				
	NA 1236C > T [92, 116, 124]					
	NA 2677G > T/A [92, 115, 116, 124]					
	NA 3435C > T [88, 92, 115, 116, 121, 124]					
	⬆(SN-38) diplotype 2677G-3435C[92]					
ABCC1(MRP1)	**NA** 462C > T [115]					
	NA 14008G > A [115]					
	NA 34215C > G [115]					
ABCC2	**NA** –24T > C [80, 124]					
	⬆3972T > C[86]					
	NA 33449T > C [115]					
	NA 156231A > G [124]					
	⬆*2 haplotype[91]					
	NA 1249G > A, 3972C > T [92]					
ABCG2	⬆–19572–19576[86, 124]					
	NA –19202G > C [124]					
	NA –18845T > C [124]					
	NA –18604 delA [124]					
	NA 34G > A [80,124]					
	NA 376C > T [124]					
	NA 421C > A [89, 92, 105, 124]					
	⬇421C > A[86]					
	NA 623T > C [115]					
	NA 1444A > G, 1445G > C [124]					
ATP7A			**NK**			
ATP7B			**NK**			
CTR1			**NK**			
LAT1/LAT2				**NA**[74, 75]		
hOCT2			**NA**[64]			
SLC22A16						⬆ c.146 G/G[84]
						NA c.755 T>C [84]
CyclinD1/D2/D3			**NK**			

Table 2 Influence of pharmacogenetics on the efficacy of cytotoxic drugs

	EFFICACY					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
CYP1A2					**NK**	
CYP2C19		**NK**				
CYP2D6		**NK**				
CYP2E1					**NK**	
CYP3A4	**NA** *1B: −392A > G [115, 116, 124]	**NK**			**NK**	**NK**
	NA *2: 15713T > C [116]					
	NA *3: 23172T > C [115, 116, 121]					
	NA *4: 352A > G [124]					
	NA *5: 653C > G [124]					
	NA *6: 831 insA [124]					
	NA *17: 15615T > C [116, 121]					
	NA *18: 20070T > C [116, 121]					
	NA *1G, *16B, *18B [93]					
CYP3A5	**NA** *3C: 22893G > A [115, 116, 121, 124]	**NK** 3A5*1/*1 [61,69,70]			**NK**	
	NA *6: 30597G > A [115, 116, 124]	**NK** 3A5*1/*3 [61,69,70]				
	NA 6986 A>G [88]	**NK** 3A5*1/*6 [61,69,70]				
		NK 3A5*3/*3 [61,69,70]				
		NK 3A5*1/*7 [61,69,70]				
GST			**NK**	**NK**	**NK**	**NA** GSTM1 null [85]
						NA GSTT1 null [85]
UGT	**NA** 1A1*6: 211G > A [101, 102, 109, 118]				**NK**	
	NA 1A1*6: 211G > A [107, 111]					
	NK 1A1*6 [87, 89, 90]					
	NA 1A1*7: 1456T > G [107, 111, 115, 118]					
	NA 1A1*27: 686C > A [107, 109, 111]					
	NA 1A1*28: (TA)7TAA [88,89,94,101,103,106,114,118,121,124]					
	NA 1A1*28: (TA)7TAA [86, 90, 91, 108, 109, 110, 116, 117]					
	NA 1A1*35: 1291T > C [107]					
	NA 1A1*36: (TA)5TAA [121]					
	NA 1A1*37: (TA)8TAA [103]					
	NA 1A1: −3156G>A [88, 109]					
	NA 1A1: 686C > T [113]					
	NA 1A6*2: 19T > G, 541A > G, 552A > C [103]					
	NA 1A7*2: 387T > G, 391C > A, 392G > A [102]					
	⬆1A7*2: 387T > G, 391C > A [103]					
	NA 1A7*3: 387T>G, 391C>A, 392G>A, 622T>C [102]					
	⬆1A7*3: 387T > G, 391C > A, 622T > C [103]					
	NA 1A7*4: 622T > C [102]					
	NA 1A7: 33C>A,343G>A,387T>G,391C>A, 392G>A,417G>C,582T>C [86]					
	NA 1A7*2: 387T > G, 391C > A [107]					
	NA 1A7*2: 387T > G, 391C > A [122]					
	NA 1A7*3: 387T > G, 391C > A, 622T > C [107]					
	NA 1A7*3: 387T > G, 391C > A, 622T > C [122]					

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate that the gene is not related to the pharmacokinetics of the drug.

Table 2 (continued)

	EFFICACY					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
UGT	**NA** 1A7*4: 622T > C [107]					
	NA 1A7*4: 622T > C[122]					
	NA 1A7*5: (G115S) [122]					
	NA 1A7*6: (E139D) [122]					
	NA 1A7*7: 387T > G, 391C > A, (E139D) [122]					
	NA 1A7*8: 387T>G, 391C>A, (E139D), 622T>C [122]					
	NA 1A7*9: (G115S), 387T > G, 391C > A [122]					
	NA 1A9*2 [86]					
	NA 1A9*3: 98T > C [117]					
	NA 1A9*3: 98T > C [86]					
	NA 1A9*5: 766G > A [117]					
	⬆1A9–118 (dT)9/9[103]					
	⬇Haplotype: UGT1A1*1,UGT1A6*1, UGT1A7*1,UGT1A9–118(dT)10/10 [103]					
	NA 1A9*2: 8G > A [122]					
	NA 1A9*3: 98T > C [122]					
	NA 1A9*5: 766G > A [112]					
CBR1						**NA** c.219G>C [79]
						NK c.627C/C [79]
						NK 967 G/G [79]
						NK Diplotype (c.627C,+967G)[79]
						NK 1096 G/G [80]
						NK V88I [82]
						NA P131S [82]
CBR3						**NA**[79]
CES1	**NA** 1440 A>T [115]					
	NA 1525 A>C [115]					
CES2	**NA** 1647 C>T [115]					
	NA *1: 803C>G, 8721G>A, 9938G>A, 9943C>A [104]					
	NA *2: 8721G > A [104]					
	NA *3: 8721G>A, 9607C>T, 9624A>G, 9938G>A, 9943C>A [104]					
	NA *4: 8721G > A, 9938G > A, 9943C > A [104]					
	NA *7: 4595T > C [104]					
	NA *8: 7339G > A [104]					
	NA *10: 1216T > C, 9938G > A, 9943C > A [104]					
	NA Haplotype 50-UTR-363, Intron1 + 1361 [123]					
	NA Haplotype 50-UTR363,Intron1+947, Intron1+1361,Intron1+1643 [123]					
VDR					**NK**	
MDR1		**NA** C3435T [62]	**NA**[66]		⬆G571A [72]	**NA** G571A [72]
		NA G2677T [62]			**NK** 3435C/C [77]	⬇G1199A[83]
		⬇G1199A [71, 83]			⬆3435 C/C[78]	**NA** G1199A [71]

Table 2 (continued)

					2677G-3435C[78]	
MRP1			**NA**[66]			**NK** Gly671Val G/T, T/T [81]
MRP2			**NA**[66]			**NK** Haplotype Val1188GluCys 1515Tyr [81]
ABCB1(MDR1)	**NA** Haplotype: 1236C>T,2677G>T, and 3435C>T[119]	**NA** 893-Ser [63]				
	NA 1236C > T [92, 115, 116, 124]	**NA** 893-Thr [63]				
	NA 2677G > T/A [92, 115, 116, 124]					
	NA 3435C > T [88, 92, 115, 116, 121, 124]					
ABCC1(MRP1)	**NA** 462C > T [115]					
	NA 14008G > A [115]					
	NA 34215C > G [115]					
ABCC2	**NA** –24T > C [92,124]					
	NA 3972T > C [86]					
	NA 33449T > C [115]					
	NA 156231A > G [124]					
	NA *2 [92]					
	NA 1249G > A, 3972C > T [92]					
ABCG2	**NA** –19572–19576 [86,124]					
	NA –19202G > C [124]					
	NA –18845T > C [124]					
	NA –18604 delA [124]					
	NA 34G > A [92,124]					
	NA 376C > T [124]					
	NA 421C > A [86, 89, 92, 105, 124]					
	NA 623T > C [115]					
	NA 1444A > G, 1445G > C [124]					
ATP7A			**NK**			
ATP7B			**NK**			
CTR1			**NK**			
LAT1/LAT2				**NA** [74, 75]		
hOCT2			**NA** [64]			
SLC22A16						**NK** c.146 G/G [84]
						NA c.755 T>C [84]
CyclinD1/D2/D3			**NA** [67]			

Table 3 Influence of pharmacogenetics on the toxicity of cytotoxic drugs

	TOXICITY					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
CYP1A2					**NK**	
CYP2C19		**NK**				
CYP2D6		**NK**				
CYP2E1					**NK**	
CYP3A4	**NA** *1B: –392A > G [115, 116, 124]	**NK**			**NK**	**NK**
	NA *2: 15713T > C [116]					
	NA *3: 23172T > C [115, 116, 121]					
	NA *4: 352A > G [124]					
	NA *5: 653C > G [124]					
	NA *6: 831 insA [124]					
	NA *17: 15615T > C [116, 121]					
	NA *18: 20070T > C [116, 121]					
	NA *1G, *16B, *18B [93]					
CYP3A5	**NA** *3C: 22893G > A [115, 116, 121, 124]	**NK** 3A5*1/*1 [61,69,70]			**NK**	
	NA *6: 30597G > A [115, 116, 124]	**NK** 3A5*1/*3 [61,69,70]				
	NA 6986 A>G [88]	**NK** 3A5*1/*6 [61,69,70]				
		NK 3A5*3/*3 [61,69,70]				
		NK 3A5*1/*7 [61,69,70]				
GST			**NA** M1,T1,Z1 [65]	**NK**	**NK**	**NA** GSTM1 null[85]
			⬇M3*B[65]			**NA** GSTT1 null[85]
			⬇P1 G/G [65]			
			⬆P1 A/G, A/A[65]			
			⬇P1 105Val /105Val [73]			
			⬆P1105Ile /105Ile[73]			
UGT	**NA** 1A1*6: 211G > A [101, 102, 109, 118]				**NK**	
	NA 1A1*6: 211G > A [107, 111]					
	⬆1A1*6 G/G[87, 89]					
	⬆diplotype with 1A1*6[90]					
	NA 1A1*7: 1456T > G [107, 111, 115, 118]					
	NA 1A1*27: 686C > A [107, 109, 111]					
	NA 1A1*28: (TA)7TAA [88,89,90,91,94,103,106,108,110,117,121,124]					
	⬆1A1*28: (TA)7TAA[101]					
	⬆ 1A1*28: (TA)7TAA [86, 109, 116, 118]					
	⬆ 1A1*28: (TA)7TAA[114]					
	NA 1A1*35: 1291T > C [107]					
	NA 1A1*36: (TA)5TAA [121]					
	NA 1A1*37: (TA)8TAA [103]					
	⬆ 1A1: –3156A/A[88, 109]					
	NA 1A1: 686C > T [113]					
	NA 1A6*2: 19T > G, 541A > G, 552A > C [103]					
	NA 1A7*2: 387T > G, 391C > A, 392G > A [102]					

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate that the gene is not related to the pharmacokinetics of the drug.

Table 3 (continued)

	TOXICITY					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
UGT	⬇1A7*2: 387T > G, 391C > A[103]					
	NA 1A7*3: 387T>G,391C>A,392G>A,622T>C[102]					
	⬇1A7*3: 387T > G, 391C > A, 622T > C[103]					
	NA 1A7*4: 622T > C [102]					
	NA 1A7: 33C>A,343G>A,387T>G, 391C>A,392G>A,417G>C,582T>C [88]					
	NA 1A7*2: 387T > G, 391C > A [107]					
	NA 1A7*2: 387T > G, 391C > A [122]					
	NA 1A7*3: 387T > G, 391C > A, 622T > C [107]					
	NA 1A7*3: 387T > G, 391C > A, 622T > C [122]					
	NA 1A7*4: 622T > C [107]					
	NA 1A7*4: 622T > C [122]					
	NA 1A7*5: (G115S) [122]					
	NA 1A7*6: (E139D) [122]					
	NA 1A7*7: 387T > G, 391C > A, (E139D) [122]					
	NA 1A7*8:387T>G,391C>A,(E139D),622T>C[122]					
	NA 1A7*9: (G115S), 387T > G, 391C > A [122]					
	NA 1A9*2 [86]					
	NA 1A9*3: 98T > C [117]					
	NA 1A9*3: 98T > C [86]					
	NA 1A9*5: 766G > A [117]					
	⬇1A9–118 (dT)9/9[103]					
	NA Haplotype: UGT1A1*1,UGT1A6*1, UGT1A7*1,UGT1A9–118(dT)10/10 [103]					
	NA 1A9*2: 8G > A [122]					
	NA 1A9*3: 98T > C [122]					
	NA 1A9*5: 766G > A [112]					
CBR1						**NA** c.219 G>C[79]
						NK c.627 C/C[79]
						NK 967 G/G [79]
						NK Diplotype (c.627,+967G)[79]
						NK 1096 G/G[80]
						NK V88I [82]
						NA P131S [82]
CBR3						**NA**[79]
CES1	**NA** 1440 A>T [115]					
	NA 1525 A>C [115]					
CES2	**NA** 1647 C>T [115]					
	NA *1: 803C>G,8721G>A,9938G>A,9943C>A[104]					
	NA *2: 8721G > A [104]					
	NA *3: 8721G>A, 9607C>T, 9624A>G, 9938G>A, 9943C>A [104]					

Table 3 (continued)

	TOXICITY					
	IRINOTECAN	**VINCRISTINE**	**CISPLATIN**	**MELPHALAN**	**ETOPOSIDE**	**DOXORUBICIN**
CES2	**NA** *4: 8721G > A, 9938G > A, 9943C > A [104]					
	NA *7: 4595T > C [104]					
	NA *8: 7339G > A [104]					
	NA *10: 1216T > C, 9938G > A, 9943C > A [104]					
	NA Haplotype 50-UTR-363, Intron1 + 1361 [123]					
	NA Haplotype 50-UTR-363,Intron1+947, Intron1+1361,Intron1+1643 [123]					
VDR					**NK**	
MDR1		**NA** C3435T [62]	**NK**		⬆G571A[72]	**NA** G571A[72]
		NA G2677T[62]			**NK** 3435 C/C[77,78]	**NK** G1199A[83]
		NK G1199A [71]			**NK** 2677 G/G[77]	**NA** G1199A[71]
		⬆G571A[72]			**NA** G2677T[78]	**NK** G1199T[83]
		NK G1199T [83]			**NK** Haplotype 2677G-3435C [78]	
MRP1			**NK**			⬆Gly671Val G/T, T/T[81]
MRP2			**NK**			⬆haplotype Val1188Glu-Cys1515Tyr[81]
ABCB1(MDR1)	**NA** Haplotype: 1236C>T, 2677G>T and 3435C>T [119]	**NA** 893-Ser [63]				
	NA 1236C>T [92, 115, 116, 124]	**NA** 893-Thr [63]				
	NA 2677G > T/A [92, 115, 116, 124]					
	NA 3435C > T [88, 92, 115, 116, 121, 124]					
	⬆2677G/G[92]					
	⬆3435T/T[92]					
ABCC1(MRP1)	**NA** 462C > T [115]					
	NA 14008G > A [115]					
	NA 34215C > G [115]					
ABCC2	**NA** –24T > C [92, 124]					
	NA 3972T > C [86]					
	NA 33449T > C [115]					
	NA 156231A > G [124]					
	⬇*2 [91]					
	NA 1249G > A, 3972C > T [92]					
ABCG2	**NA** –19572–19576 [86, 124]					
	NA –19202G > C [124]					
	NA –18845T > C [124]					
	NA –18604 delA [124]					
	NA 34G > A [92, 124]					
	NA 376C > T [124]					
	NA 421C > A [86, 89, 92, 105, 124]					
	NA 623T > C [115]					
	NA 1444A > G, 1445G > C [124]					
ATP7A			**NK**			
ATP7B			**NK**			
CTR1			**NK**			
LAT1/LAT2				**NA**[74, 75]		
hOCT2			**NA**[64]			
SLC22A16						**NK** c.146 G/G [84]
						NA c.755 T>C [84]
CyclinD1/D2/D3			**NK**			

Table 4 Influence of pharmacogenetics on the pharmacokinetic profile of drugs in clinical development

	EXPOSURE						
	17AAG	**APREPITANT**	**BMS-536924**	**EFLORNITHINE**	**IMATINIB**	**NUTLIN3**	**ONCOLYTIC VIRUS**
CYP1A2		**NK**			**NK**		
CYP2C9					**NA** [99]		
CYP2C19		**NK**			**NA** [99]		
CYP2D6					**NA** 2D6*4 [99]		
CYP3A4	**NK**	**NK**			**NA** [99]		
CYP3A5	⬆3A5*3 (homozygous) [96]				**NA** [99, 100]		
ABCB1 (Pgp)					**NA** [99]	**NK**	
					⬇1236 TT [100]		
					⬇2677 TT [100]		
					⬇3435 TT [100]		
ABCG2					**NA** [99]		
NQO1	**NA** NQO1*2 [96]						

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate the gene is not related to the pharmacokinetics of the drug.

Table 5 Influence of pharmacogenetics on the efficacy of drugs in clinical development

	EFFICACY						
	17AAG	**APREPITANT**	**BMS-536924**	**EFLORNITHINE**	**IMATINIB**	**NUTLIN3**	**ONCOLYTIC VIRUS**
CYP1A2		**NK**			**NK**		
CYP2C9					**NA** [99]		
CYP2C19		**NK**			**NA** [99]		
CYP2D6					**NA** 2D6*4 [99]		
CYP3A4	**NK**	**NK**			**NA** [99]		
CYP3A5	**NA** 3A5*3 [96]				**NA** [99, 100]		
ABCB1 (Pgp)					**NA** [99]	**NK**	
					NA 1236 TT [100]		
					NA 2677 TT [100]		
					NA 3435 TT [100]		
ABCG2					**NA** [99]		
NQO1	⬇NQO1*2 [95,96,97,98]						

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate that the gene is not related to the pharmacokinetics of the drug.

Table 6 Influence of pharmacogenetics on the toxicity of drugs in clinical development

	TOXICITY						
	17AAG	**APREPITANT**	**BMS-536924**	**EFLORNITHINE**	**IMATINIB**	**NUTLIN3**	**ONCOLYTIC VIRUS**
CYP1A2		**NK**			**NK**		
CYP2C9					**NA** [99]		
CYP2C19		**NK**			**NA** [99]		
CYP2D6					**NA** 2D6*4 [99]		
CYP3A4	**NK**	**NK**			**NA** [99]		
CYP3A5	**NA** 3A5*3 [96]				**NA** [99, 100]		
ABCB1 (Pgp)					**NA** [99]	**NK**	
					NA 1236 TT [100]		
					NA 2677 TT [100]		
					NA 3435 TT [100]		
ABCG2					**NA** [99]		
NQO1	**NA** NQO1*2 [96]						

* "⬆" indicates an increase in drug exposure, efficacy or toxicity;

† "⬇" indicates a decrease in drug exposure, efficacy or toxicity;

‡ "**NA**" indicates that there is no association between the corresponding gene and the pharmacokinetics of the drug;

§"**NK**" (Not Known) indicates that pharmacogenetic data have not been found in the published literature;

‖ "grey cells" indicate that the gene is not related to the pharmacokinetics of the drug.

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