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

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DO PHARMACOKINETIC POLYMORPHISMS EXPLAIN TREATMENT FAILURE IN HIGH-RISK PATIENTS WITH NEUROBLASTOMA?

ABSTRACT

Purpose: Neuroblastoma is the most common extra cranial solid tumour in childhood. It accounts for the 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 less than 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: Literature search based on Pubmed's database Medical Subject Headings (MeSH) has been performed to retrieve all pertinent publications on current treatment options and on new classes of drugs under investigation. 158 articles have been reviewed and relevant data have been extracted and summarised.

Results and conclusions: Few of the large number of polymorphisms identified showed an effect on pharmacokinetics which could be considered clinically relevant. Despite clinical relevance, none of the single nucleotide polymorphisms (SNPs) investigated so far can explain treatment failure. These findings seem to reflect the clinical context, in which these drugs are used, i.e., in combination with multimodal therapy. In addition, many of the pharmacogenetic studies do not assess (differences in) drug exposure, which could contribute to explaining pharmacogenetic associations. Regardless of the evidence that new classes of drugs show significant activity on all neuroblastoma cell lines, it remains unclear whether such activity translates into clinical efficacy, irrespective of resistance or MYCN amplification. Elucidation of the clinical value of pharmacogenetic factors in the treatment of neuroblastoma demands an integrated pharmacokinetic-pharmacodynamic approach to treatment response.

KEYWORDS

Neuroblastoma, pharmacogenetics, pharmacokinetics, cytotoxic drugs, model-based approach.

1 INTRODUCTION

1.1 Neuroblastoma

Neuroblastoma (NB) is the most common extra cranial solid tumour in childhood, it belongs to the “small blue round cells” neoplasms, and it accounts for the 15% of all paediatric oncology deaths¹⁻³. Its incidence peaks at age 0 to 4 years, and less than 5% of patients are over the age of 10 years². It is a neuroendocrine tumour tightly connected to the sympathetic nervous system. Given that it originates from the primitive neuroepithelial cells of the neural crest, it can develop anywhere in the sympathetic system. 50% of primary tumours arise in the adrenal medulla, but other common sites of disease are neck, chest, abdomen and pelvis. At the diagnosis, in most cases, neuroblastoma has already metastasised, and usually metastasis affects liver, bones, bone marrow, lymph nodes and skin¹⁻³.

The aetiology of neuroblastoma is still poorly understood. Few causative factors have been identified for the neoplasm: familiar forms are rare (about 1%); there is not a 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, and strikingly, in a 5% of cases, it manifests a spontaneous regression. Prognosis, in the same way, ranges from overall survival to high risk for fatal demise. Because of the tumour heterogeneity the use of biomarkers has been required to select

the appropriate treatment schedule according to a risk-group classification. MYCN amplification, chromosomal loss (1p) or gain (17q), DNA index (near diploid), age older than 18 months, and “International Neuroblastoma Staging System” (INSS) stages III and IV are all predictors of poor prognosis and disease malignancy¹⁻⁷. Like MYCN, many other biomarkers have been studied to specify patient stratification: e.g., the Trk family of neurotrophin receptors, an 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. Up to now, only the amplification of the oncogene MYCN can be considered as an independent marker to assess tumour status and treatment outcome^{1;2}. In this manner according to tumour behaviour and biomarker prediction there is a risk group classification of the disease, and therefore of treatment protocols.

Although in the last 20 years this approach substantially improved treatment outcome for low- and intermediate-risk patients, up to date there has been little improvement in the high-risk patient group. In spite of intensive poly-therapy, high-risk patients still have an overall survival rate of 30-40%^{1;3}.

Several reasons could explain the low overall survival rate. Considering that important associations have been demonstrated between pharmacogenetics and efficacy in different solid tumours (i.e., the use of Herceptin in the treatment of HER2 positive breast cancers with benefits in terms of disease free survival and

overall survival⁸⁻¹⁰), the aim of this review is to explore the role of pharmacogenetics in the treatment of neuroblastoma. Two main questions to be addressed are whether pharmacogenetic differences (partly) explain treatment failure and whether model-based interventions, such as different dosing algorithms, may improve the outcome of therapy and the safety profiles in high-risk patients.

1.2 Pharmacogenetics

In the context of our review the term pharmacogenetics will be 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, and pharmacogenetics is a subset of pharmacogenomics and is defined as the influence of variations in DNA sequence on drug response⁸. Pharmacogenetics is a relatively new field of research, which aims to improve the medical knowledge using DNA sequence information^{11;12}.

Clinical research on prognostic, risk and covariate factors often assigns a privileged position to pharmacogenetics compared to 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 mis-interpretation of the findings. A too narrow

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 which can influence pharmacokinetics, pharmacodynamics and clinical response, and that these factors can interact with each other.

This review represents an effort to answer the previous questions by evaluating the role of pharmacogenetics on the pharmacokinetic properties of the cytotoxic drugs used in the current treatment of neuroblastoma, and by highlighting the requirements to evaluate its role in new therapeutic approaches. In addition, based on our findings, suggestions are given for alternative therapeutic approaches, which can potentially reduce treatment failure.

2 METHODS

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

First, attention has been given to the cytotoxic drugs used for the current treatment of neuroblastoma. Initially, the drug's generic name was associated to four general keywords: pharmacokinetics, pharmacogenetics, neuroblastoma,

and leukaemia, whilst during a second step, the drug name was associated to specific elements of drug disposition.

Secondly, new classes of drugs, which are 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 have been retrieved from paediatric studies, and especially from patients affected by neuroblastoma or leukaemia¹³⁻⁶⁰. Differently, pharmacogenetic data have been gathered from any available study⁶¹⁻¹²⁴. We have decided to exclude references related to genetic variations in pharmacodynamics and disease.

A total of 158 articles and reviews have been 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).

3 RESULTS

3.1 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. Chemotherapy 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; second, during myeloablative chemotherapy (or high-dose CT) in association with stem cell transplantation aim to consolidate induction CT and surgery³.

Despite the various approaches to treatment high-risk groups have a very low overall survival 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 and pharmacodynamics of six of the main cytotoxic drugs used in neuroblastoma treatment has been evaluated.

Without taking into account the nature of treatment as adjuvant therapy, it was found that only few SNPs show a relevant effect on pharmacokinetics. In agreement with our hypothesis, published results seem to confirm that a 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 will be briefly highlighted in the following paragraphs.

3.1.1 IRINOTECAN

Up to date UGT1A1*28 is the only SNP introduced in a label (US) among all cytotoxic drugs included in this review. It is noteworthy to underline that the UGT1A is the main enzyme in controlling the deactivation of 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 to a single agent treatment with Irinotecan, have a higher exposure to the active metabolite and are at increased risk for neutropenia⁸. In fact, various publications seem to confirm higher exposure to SN-38^{86;90;91;108-110;116;117;120} and the increased risk for neutropenia^{86;101;109;114;116;118} 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, showed higher exposure to the active metabolite^{87;89;90;107;111} and an increased risk for neutropenia^{87;89;90}. However, further studies are needed to assess the clinical value of UGT1A1*6.

3.1.2 VINCRIStINE

According to Dennison et al.^{61;70}, and Renbarger et al.⁶⁹, CYP3A4 and CYP3A5 play a key role in metabolising vincristine to the main metabolite (the secondary

amine M1), with a 9- to 14-fold higher selectivity for the CYP3A5. As mentioned before, having a key role in the metabolic pathway is an essential requirement in order to influence the pharmacokinetic profile of a drug. Although in the study from 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 does contribute to the inter-individual variability in vincristine metabolism.

3.1.3 OTHER CYTOTOXIC DRUGS

None of the SNPs analysed so far seem to affect the pharmacokinetic profile of cisplatin, melphalan, etoposide and doxorubicin in a way that can be considered clinically relevant.

3.2 DRUGS IN CLINICAL DEVELOPMENT

To significantly improve the treatment of neuroblastoma several studies have been carried out to evaluate the potential of novel therapeutic alternatives. New approaches to circumvent the high resistance of NB cells to chemotherapy could have a great impact on future treatment options. Seven new classes of drugs have been identified which may contribute to that objective. Mechanisms of action, metabolic pathway, and efficacy on NB cells have been analysed, with

particular attention to pharmacogenetic effects. Tables 4, 5, and 6 provide a summary of the findings from published pharmacogenetic studies.

3.2.1 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 over-expressed in tumour cell lines¹²⁵. The great advantage of Hsp90 inhibitors should be the simultaneous depletion of multiple oncogenic client proteins¹²⁶. Kang et al.¹²⁵ demonstrated the inhibition of SK-N-SH and LAN-1 NB cell line growth by 17-AAG, accompanied by reduced levels of Raf-1 and Akt protein kinases.

On the other hand, Jayanthan et al.¹²⁶ showed that all NB 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 the 17-AAG with an IC50 value ranging from 0.5 to 5 µM across different cell lines. In the same study 17-AAG also sensitised NB cells to various chemotherapeutic agents.

17-AAG is metabolised by CYP3A4 and CYP3A5 to the active metabolite 17-AG, and by NAD(P)H dehydrogenase quinone 1 (NQO1) to the very active metabolite 17-AAGH2. The SNP NQO1*2, which seems to delete the enzyme activity, induces a 32-fold increase in 17-AAG resistance^{97;98}, which suggests that such variation could have a relevant effect on the clinical response. However further studies are needed to characterise the role of NQO1 and of other related polymorphisms in 17-AAG metabolic pathway. However, polymorphisms

affecting CYP450 do not influence the pharmacokinetics of 17-AAG because the metabolite has a similar activity to the parent compound.

3.2.2 APREPITANT

The activation of neurokinin 1 (NK1) receptor by substance P induces mitogenesis, and regulates the active migration of tumour cells and angiogenic process, besides regulating many biological functions implicated in neurogenic inflammation, pain and depression. Aprepitant, a specific inhibitor of NK1, could inhibit both DNA synthesis and cell proliferation through the mitogen-activated protein kinase (MAPK) pathway¹²⁷.

In the study from Muñoz et al.¹²⁷ aprepitant showed a cytotoxic activity on all glioma, neuroblastoma, retinoblastoma, pancreatic carcinoma, larynx carcinoma, gastric carcinoma and colon carcinoma cell lines tested, and after its administration a great number of apoptotic cell 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 tables 2A, 2B and 2C, data on pharmacogenetic variation has not been reported.

3.2.3 BMS-536924

Insuline-like growth factor (IGF), through the IGF-1 receptor, regulates many cellular survival mechanisms, such as cellular growth, differentiation, apoptosis, tumour angiogenesis and metastasis, and different tumour types have shown the over-expression of this receptor¹²⁸.

All NB cell lines tested in the study from Huang et al.¹²⁸ were sensitive to the treatment with BMS-536924 (IC₅₀ 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 (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.

3.2.4 EFLORNITHINE (alpha-difluoromethylornithine)

Polyamines, essential molecules for cellular activity, are undoubtedly involved in tumour cell growth¹²⁹. If their synthesis is inhibited, cell growth is stopped or severely retarded. One of the hallmarks of NB MYCN-amplified cell lines is the polyamine expansion¹³⁰.

Ornithine decarboxylase (ODC1) is a key enzyme in the biosynthetic pathway of polyamines, and ODC1 high levels correlate with poor outcome in neuroblastoma. Eflornithine (DFMO) has been shown to induce cell cycle arrest (G1) inhibiting ODC1, in NB cell lines. The underlying cause is a polyamine depletion which arrests the cell cycle through the cyclin-dependent kinase inhibitor (p27kip1) pathway. Wallick et al.¹²⁹ demonstrated its inhibitory activity on NB cell lines LAN-1 and NMB-7 with a near-total cessation of cellular growth after three days. While Koomoa et al.¹³¹ confirmed the inhibition of LAN-1 proliferation,

in the study from Rounbehler et al.¹³² DFMO preferentially abolished the growth of MYCN-amplified cell lines. DFMO also increased the effects of chemotherapy without additional toxicity¹³⁰. It is important to point out that the polyamine depletion, besides the cell cycle arrest, also induces through the PI3K/Akt pathway a mechanism of cell survival which could explain a possible moderate efficacy of DFMO alone.

Eflornithine is not metabolised and pharmacogenetic information pertinent to drug disposition is not available so far.

3.2.5 IMATINIB MESYLATE

The 2-phenylaminopyrimidine imatinib is a specific inhibitor of tyrosine kinase enzymes. It binds the TK domain of Abl, c-kit (or CD117), and PDGF-R. C-kit and PDGF-R have been detected in neuroblastoma¹³³⁻¹³⁵, and the cytokine receptor seems to be expressed mainly in the most aggressive forms of the tumour¹³⁶. PDGF plays an important role in controlling growth, differentiation and survival of glial cells and immature neuroblasts, whilst c-kit is essential for normal haematopoiesis, gametogenesis, and melanogenesis¹³⁵. *In vitro* studies from Vitali et al., Beppu et al., Rossler et al., and Palmberg et al.¹³³⁻¹³⁶ 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 ABC transporters, Pgp and ABCG2. The common polymorphisms associated with these routes only have a limited influence on the imatinib pharmacokinetics, and

therefore do not seem to be the underlying cause of the high inter-individual variability observed in clinical data^{99;137}.

3.2.6 NUTLIN 3

MDM2 is a negative regulator of p53. It prevents p53-control on cell cycle and apoptosis, inhibiting the transcriptional activation of the tumour suppressor. However, the effectiveness of an inhibitor of MDM2 is evident only if p53 is functional. Given this prerequisite, it is important to highlight that less than 2% of NB tumours exhibit mutations on TP53 gene¹³⁸.

Nutlin 3 is a specific chiral inhibitor of MDM2, which induces G1 cell cycle arrest, apoptosis and neuronal differentiation in neuroblastoma cells¹³⁸⁻¹⁴¹, with an IC50 value of 3.25 $\mu\text{mol/L}$ ¹⁴². The 3a enantiomer shows a ~200-fold higher affinity for MDM2 than the enantiomer 3b¹⁴². Nutlin 3 is also a Pgp substrate and both enantiomers increase the cytotoxic activity of anticancer agents which are also substrate of Pgp (e.g., Vincristine)¹⁴¹. No pharmacogenetic information is available for this compound.

3.2.7 ONCOLYTIC VIRUS

Oncolytic viruses represent a new important therapeutic approach in cancer treatment¹⁴³⁻¹⁴⁶. They can circumvent chemotherapy-induced resistance mechanism through a specific lysis of tumour cells. In addition, evidence exists of their efficacy and safety in clinical trials¹⁴⁷⁻¹⁴⁹. They basically act by inducing cell lysis and genetic mutations applied to their genome restrict the viral replication

only to the tumour cells. An interesting feature of these viruses is the opportunity to achieve an additional mechanism of action arming the virus against specific targets (examples are listed below).

NB cells showed 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 the tumour relapse¹⁴⁷. Neuroblastoma is also highly susceptible to HSV-mediated oncolysis^{148;150;151}, and the HSV virus represents the best solution for a possible application in NB treatment.

Nestin, a protein expressed in nerve cells and involved in the radial growth of the axon, is one of the possible options to arm an oncolytic virus. Thomas et al.¹⁵² and Mahller et al.¹⁴⁷ demonstrated a correlation between nestin expression and MYCN amplification, whereas the same correlation has not been shown in the study from Korja et al.¹⁵³ In the study from Mahller et al. rQNestin34.5 oHSV abolished tumour formation for more than 60 days in mice affected by neuroblastoma¹⁴⁷.

Other possible options, besides the nestin targeted vector, are HSV viruses armed with immunomodulatory molecules (B7-1, IL12, and IL18), armed against the activated 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.^{148;149;151}. No pharmacogenetic data have been found for this class of drugs.

4 DISCUSSIONS AND CONCLUSION

To date, limited improvement in survival rates has been achieved for high-risk patients with neuroblastoma. In this review we have explored whether pharmacogenetic variation in pharmacokinetics could explain treatment failure and have attempted to highlight some of the research gaps in the evaluation of novel molecules for the treatment of neuroblastoma. Numerous pharmacogenetic studies have been proposed in the last ten years, but most of them are basically related to drug disposition.

Based on the published literature, pharmacokinetic polymorphisms do not seem to be the cause of the low survival rate in NB. None of the SNPs analysed so 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., the response is the result of a multimodal approach to NB). Furthermore, it can be derived from the low therapeutic failure in low- and intermediate-risk patients that the presence of pharmacokinetic polymorphisms in those groups does not seem to 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) and pharmacodynamic variants itself may ultimately underlie differences in response rate.

In addition, we have shown that only few out 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 and increase in exposure to the active metabolite SN-38 and consequently the risk for neutropenia. Moreover, according to Renbarger et al. and Dennison et al., polymorphisms affecting the CYP3A5 could significantly alter the pharmacokinetics of vincristine, given that this isozyme plays a key role in the elimination of vincristine. The same can be assumed from the investigation by Kelland et al. and Guo et al. on NQO1. This enzyme metabolises 17AAG to the very active metabolite 17AAGH₂; and the polymorphic variant NQO1*2, which cause 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 and especially on the enzyme contribution to the overall metabolic rate 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 assess the potential consequences of genetic polymorphisms. Given that compensatory pathways are involved in the disposition of the majority of the drugs suitable for clinical use, it can be

anticipated that pharmacogenetic variation in ADME will often have limited impact on variability in pharmacodynamics and response. This is one of the reasons why 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, taking into account the neuroblastoma, most of the 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 have to be taken into account in oncology.

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 those drugs under clinical investigation, our review reveals the identification of compounds with a prominent pharmacological activity on neuroblastoma cells, irrespective of level of resistance and MYCN amplification. Between 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 say whether such activity translates into clinical efficacy and further studies are needed to confirm the clinical value of novel classes of drugs in NB treatment. Moreover, an effective drug combination and dosing algorithm still need to be identified to ensure maximum effectiveness for most compounds.

Going back to the role of pharmacogenetics, the review shows the importance of the context in which the drug is used in 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 could probably lead to biased results. All relevant covariates should be considered in the implementation of a clinical study and included in the statistical analysis. In this sense, many of the pharmacogenetic studies summarised in this review have not considered such an integrated approach or include details on 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 polymorphisms clinical response and as such, should become best practice in the analysis of pharmacogenetic data¹⁵⁴⁻¹⁵⁸.

Model-based drug development comprises the use of mathematical and statistical concepts which describe longitudinal data (i.e., a disease model), exposure-response relationships (i.e., PKPD model) and clinical trial design (implementation model). 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 variable (e.g. C_{max}), which are often prone to experimental artefacts. Also, sparse, rather than rich frequent sampling can be used in population PK or PKPD models. In this sense, modelling represents a strategy for translating the clinical implications of pharmacogenetic variation. And most importantly, a model-based approach can support the selection and individualisation of effective dosing regimens, which may be more critical than the presence of ADME polymorphism in high-risk patients with neuroblastoma.

CONFLICT OF INTEREST STATEMENT

There are no arrangements of financial nature, or of any other kind, that could lead to conflict of interests with regard to this manuscript.

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TABLE 1: Influence of pharmacogenetics on the exposure profile of cytotoxic drugs;

	EXPOSURE			
	IRINOTECAN	VINCRIStINE	CISPLATIN	MELPHALAN
CYP1A2				
CYP2C19		NK		
CYP2D6		NK		
CYP2E1				
CYP3A4	NA *1B: -392 A > G ^{115, 116, 124}	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}		
	NA *6: 30597G > A ^{115, 116, 124}	↓3A5*1/*3 ^{61,69,70}		
	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
UGT	NA 1A1*6: 211G > A ^{101, 102, 109, 118}			
	↑(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			
	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				
CBR3				
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				
VDR					
MDR1		NA C3435T ⁶²	NK		
		NA G2677T ⁶²			
		NK G1199A ^{71,83}			
		NK G571A ⁷²			
		NK G1199T ⁸³			
MRP1			NK		
MRP2			NK		
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				
CyclinD1/D2/D3			NK	

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§“NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.

TABLE 2: Influence of pharmacogenetics on the efficacy of cytotoxic drugs;

	EFFICACY			
	IRINOTECAN	VINCRIStINE	CISPLATIN	MELPHALAN
CYP1A2				
CYP2C19		NK		
CYP2D6		NK		
CYP2E1				
CYP3A4	NA *1B: -392A > G ^{115, 116, 124}	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}		
	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
UGT	NA 1A1*6: 211G > A ^{101, 102, 109, 118}			
	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			
	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				
CBR3				
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				
MDR1		NA C3435T ⁶²	NA ⁶⁶	
		NA G2677T ⁶²		
		↓G1199A ^{71, 83}		
		↑G571A ⁷²		
		↑G1199T ⁸³		
MRP1			NA ⁶⁶	
MRP2			NA ⁶⁶	
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				
CyclinD1/D2/D3			NA ⁶⁷	

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§“NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.

TABLE 3: Influence of pharmacogenetics on the toxicity of cytotoxic drugs;

	TOXICITY			
	IRINOTECAN	VINCRIStINE	CISPLATIN	MELPHALAN
CYP1A2				
CYP2C19		NK		
CYP2D6		NK		
CYP2E1				
CYP3A4	NA *1B: -392A > G ^{115, 116, 124}	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}		
	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
			↓M3*B ⁶⁵	
			↓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}			
	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			

	↓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				
CBR3				
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			
VDR				
MDR1		NA C3435T ⁶²	NK	
		NA G2677T ⁶²		

		NK G1199A ⁷¹		
		↑G571A ⁷²		
		NK G1199T ⁸³		
MRP1			NK	
MRP2			NK	
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				
CyclinD1/D2/D3			NK	

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§“NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.

TABLE 4: Influence of pharmacogenetics on the exposure profile of drugs in clinical development;

	EXPOSURE				
	17AAG	APREPITANT	BMS-536924	EFLORNITHINE	IMATINIB
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
					↓1236 TT ¹⁰⁰
					↓2677 TT ¹⁰⁰
					↓3435 TT ¹⁰⁰
ABCG2					NA ⁹⁹
NQO1	NA NQO1*2 ⁹⁶				

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§ “NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.

TABLE 5: Influence of pharmacogenetics on the efficacy of drugs in clinical development;

	EFFICACY				
	17AAG	APREPITANT	BMS-536924	EFLORNITHINE	IMATINIB
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
					NA 1236 TT ¹⁰⁰
					NA 2677 TT ¹⁰⁰
					NA 3435 TT ¹⁰⁰
ABCG2					NA ⁹⁹
NQO1	↓NQO1*2 ^{95,96,97,98}				

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§ “NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.

TABLE 6: Influence of pharmacogenetics on the toxicity of drugs in clinical development;

	TOXICITY				
	17AAG	APREPITANT	BMS-536924	EFLORNITHINE	IMATINIB
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
					NA 1236 TT ¹⁰⁰
					NA 2677 TT ¹⁰⁰
					NA 3435 TT ¹⁰⁰
ABCG2					NA ⁹⁹
NQO1	NA NQO1*2 ⁹⁶				

LEGEND:

* “↑” indicates an increase in drug’s exposure, efficacy or toxicity;

† “↓” indicates a decrease in drug’s exposure, efficacy or toxicity;

‡ “NA” indicates that there are not pharmacogenetic associations between the gene and the pharmacokinetic profile of the drug;

§ “NK” (Not Known) indicates that pharmacogenetic data have not been found;

|| “grey cells” indicate that there is not correlation between the gene and the pharmacokinetic profile of the drug.