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Genotype-Guided Dosing of Cyclophosphamide-Based Chemotherapy: A Pharmacogenomic Study

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ABSTRACT

*Background: Cyclophosphamide is a prodrug alkylating agent used across breast cancer, lymphoma, pediatric oncology, and hematopoietic stem cell transplantation regimens, requiring hepatic bioactivation by CYP2B6 and CYP2C19 to form the cytotoxic effector phosphoramide mustard, balanced against detoxification by ALDH1A1 and GSTA1. Interindividual pharmacokinetic variability is substantial, but no consensus genotype-guided dosing algorithm currently exists for this drug. Objective: This narrative review synthesizes published pharmacogenomic evidence on cyclophosphamide metabolism and evaluates the feasibility of genotype-guided dosing strategies to optimize efficacy and reduce toxicity. Methods: Peer-reviewed studies addressing CYP2B6, CYP2C19, GSTA1, and ALDH1A1 polymorphisms in relation to cyclophosphamide pharmacokinetics, treatment response, and toxicity were identified and synthesized narratively, organized around bioactivation and detoxification pharmacology, pharmacokinetic genotype-exposure associations, genotype-outcome associations across breast cancer, pediatric oncology, lupus nephritis, and transplantation settings, and the practical barriers to dosing translation. Findings: CYP2B6 and CYP2C19 loss-of-function variants are repeatedly associated with reduced 4-hydroxycyclophosphamide formation and, in several cohorts, inferior treatment response, with combined CYP2C19-CYP2B6 genotyping explaining up to 47.9 percent of exposure variability in one analysis. GSTA1 and ALDH1A1 variants that impair detoxification are consistently linked to increased hematologic and hepatic toxicity, including a nearly seven-fold increased odds of severe leucopenia in GSTA1*B carriers, sometimes accompanied by improved efficacy, reflecting a genuine activation-detoxification trade-off. Autoinduction across multi-day dosing, phenoconversion from comedications, transporter gene contributions rivaling metabolic enzyme effects, disease-context specificity, and marked interethnic differences in CYP2C19 allele frequency collectively explain inconsistent replication across studies. Conclusions: Existing evidence supports a biologically plausible but not yet clinically actionable pharmacogenomic basis for cyclophosphamide dosing. Prospective, multigene, disease-context-specific validation combining germline genotyping with therapeutic drug monitoring is needed before genotype-guided cyclophosphamide dosing can be translated into formal clinical guidance.*

Keywords: *cyclophosphamide pharmacogenomics; CYP2B6 polymorphism; CYP2C19 genotype; GSTA1 and ALDH1A1 variants; genotype-guided chemotherapy dosing*

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Introduction

Cyclophosphamide remains one of the most widely prescribed alkylating agents in oncology and immunology, used in curative-intent breast cancer regimens, lymphoma and leukemia protocols, pediatric neuroblastoma therapy, and myeloablative or post-transplantation conditioning for hematopoietic stem cell transplantation (HSCT), where it also serves a graft-versus-host disease prophylaxis role [1]. Cyclophosphamide is itself an inactive prodrug that requires hepatic bioactivation, principally by cytochrome P450 2B6 (CYP2B6) and, to a lesser extent, CYP2C19, CYP3A4, and CYP3A5, to form 4-hydroxycyclophosphamide, which exists in tautomeric equilibrium with aldophosphamide before nonenzymatically decomposing into the cytotoxic effector phosphoramide mustard and acrolein, a urotoxic byproduct [2,3]. A parallel detoxification pathway converts aldophosphamide to the inactive metabolite carboxyphosphamide through aldehyde dehydrogenase 1A1 (ALDH1A1), while glutathione S-transferase A1 (GSTA1) conjugates phosphoramide mustard and its downstream reactive intermediates to glutathione, limiting cytotoxic and myelosuppressive exposure [4,5]. Because bioactivation and

detoxification are catalyzed by genetically polymorphic enzymes, interindividual variability in cyclophosphamide pharmacokinetics is substantial, with intrinsic hepatic clearance differing by more than fifty-fold across patients in some series [6].

This wide variability has direct clinical consequences: underexposure to 4-hydroxycyclophosphamide risks therapeutic failure, while overexposure increases the risk of severe myelosuppression, hemorrhagic cystitis, hepatotoxicity, and gonadotoxicity [7,8]. Unlike several other cytotoxic agents for which the Clinical Pharmacogenetics Implementation Consortium has issued formal genotype-to-dose translation tables, no consensus genotype-guided dosing algorithm yet exists for cyclophosphamide, despite two decades of pharmacogenomic investigation implicating CYP2B6, CYP2C19, GSTA1, and ALDH1A1 variants in both pharmacokinetic and clinical outcome heterogeneity [3,9]. This narrative review synthesizes the published pharmacogenomic literature on cyclophosphamide metabolism and genotype-guided dosing strategies, organizing the discussion around the molecular pharmacology of the bioactivation and detoxification pathways, the pharmacokinetic evidence linking specific genotypes to metabolite exposure, the clinical outcome data linking genotype to efficacy and toxicity across disease settings, and the practical and methodological barriers that continue to impede translation of this evidence into a validated dosing algorithm.

Molecular Pharmacology of Cyclophosphamide Bioactivation and Detoxification

Cyclophosphamide bioactivation begins with ring hydroxylation at the 4-position, a reaction catalyzed predominantly by CYP2B6 at therapeutically relevant plasma concentrations, with secondary contributions from CYP2C19, CYP3A4, and CYP3A5, and additional low-affinity activity from CYP2C9 and CYP2C8 [3,2]. The resulting 4-hydroxycyclophosphamide diffuses out of hepatocytes and into target tissues, where its tautomer aldophosphamide undergoes either further oxidation, spontaneous beta-elimination to the active phosphoramide mustard and acrolein, or detoxification by ALDH1A1 to carboxyphosphamide, an inactive metabolite excreted in urine [4]. This branch point between activation and detoxification is pharmacologically critical: tumor cells and normal tissues with relatively low ALDH1A1 expression are preferentially sensitized to cyclophosphamide's cytotoxic effector, a property long exploited in high-dose HSCT conditioning, while normal tissues with high ALDH1A1 activity, notably hematopoietic stem cells themselves, are relatively protected [9]. Downstream of phosphoramide mustard formation, GSTA1 catalyzes conjugation with reduced glutathione, and this detoxification step appears to be a dominant determinant of hematologic toxicity independent of the rate of 4-hydroxycyclophosphamide formation [5].

A further layer of complexity arises from cyclophosphamide's well-documented capacity for hepatic autoinduction: repeated dosing upregulates CYP2B6 and other activating enzymes over the course of a multi-day conditioning regimen, producing a time-dependent increase in bioactivation that a mechanism-based pharmacokinetic model first formally characterized in the context of a cyclophosphamide-thiotepa drug interaction, in which thiotepa competitively inhibited approximately eighty percent of the relevant enzymic activity [10]. This autoinduction phenomenon means that genotype-exposure relationships established after a single dose may not generalize to multi-day regimens, and it has been proposed as one explanation for the within-patient, cycle-to-cycle variability in 4-hydroxycyclophosphamide formation that has been observed even when genotype is held constant [11]. Clinically significant allele frequency differences across ancestral populations compound this pharmacological complexity: CYP2C19 loss-of-function alleles, particularly CYP2C19*2 and CYP2C19*3*, occur at substantially higher frequency in Oceanian and East Asian populations than in European populations, meaning that the clinical impact of CYP2C19-mediated bioactivation deficits is unevenly distributed across the populations in which cyclophosphamide-based regimens are prescribed worldwide [12].

Principal genes implicated in cyclophosphamide bioactivation and detoxification, their pathway role, and representative pharmacogenomic findings.

Gene	Pathway role	Key variant(s)	Representative finding	Reference
CYP2B6	Bioactivation (4-hydroxylation)	*5*, 6; promoter/intronic SNPs	54-fold interindividual difference in hepatic metabolic activity; normal/rapid metabolizers show more hepatotoxicity and hematologic toxicity	Nakajima et al. 2007; Mango et al. 2023
CYP2C19	Bioactivation (secondary)	*2*, 3 (loss of function)	Explains 23.6% of 4-OHCP AUC variance alone; combined with CYP2B6, 47.9%; *2 homozygotes show OR 0.26 for lymphoma response	Helsby et al. 2010; Helsby et al. 2019
ALDH1A1	Detoxification (aldophosphamide to carboxyphosphamide)	*2 (17-bp deletion); rs13959	ALDH1A1*2 meets genome-wide significance for poor breast cancer outcome; rs13959 TT genotype OR 6.40 for favorable response	Kalra et al. 2018; Islam et al. 2024
GSTA1	Detoxification (glutathione conjugation of phosphoramide mustard)	*B	GSTA1*B carriers show OR 6.94 for severe leucopenia; associated with higher grade III-IV acute GVHD after haploidentical HSCT	Afsar et al. 2012; Muniz et al. 2022

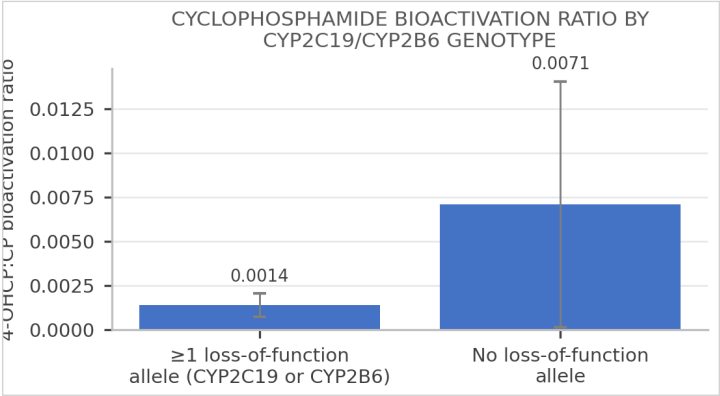
Gene	Pathway role	Key variant(s)	Representative finding	Reference
ABCC2	Transport of glutathione-conjugated metabolites	1249G>A	Heterozygous carriers show approximately 51% reduction in non-induced cyclophosphamide clearance	Kim et al. 2013

Pharmacokinetic Evidence for CYP2B6 and CYP2C19 Genotype Effects

The pharmacokinetic case for CYP2B6 as the principal determinant of cyclophosphamide bioactivation is the most extensively replicated finding in this literature. In an early study of 103 Japanese patients with lymphoma or breast cancer, Nakajima and colleagues identified CYP2B6 promoter and intronic single nucleotide polymorphisms, at positions g.-2320T>C, g.-750T>C, g.15582C>T, and g.18492T>C, that were each associated with significantly reduced conversion of cyclophosphamide to 4-hydroxycyclophosphamide, alongside a striking fifty-four-fold range of hepatic metabolic activity across the cohort [6]. Ekhart and colleagues extended this analysis across nine candidate genes, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1, and ALDH3A1, in patients receiving high-dose cyclophosphamide-containing conditioning, establishing the multigenic framework that subsequent pharmacogenomic studies of this drug have generally adopted [3]. In breast cancer patients receiving standard-dose FAC chemotherapy, Afsar and colleagues confirmed a CYP2C192 *gene-dose effect on the 4-hydroxycyclophosphamide-to-cyclophosphamide ratio, while also identifying an ALDH3A1*2-associated increase in this ratio, together illustrating that both activation and a secondary detoxification enzyme independently shape systemic exposure to the active metabolite [5].

The most mechanistically direct demonstration of a combined CYP2C19-CYP2B6 effect came from in vitro human liver microsome studies paired with clinical data from patients with lupus nephritis: livers carrying at least one loss-of-function allele at either gene showed significantly reduced intrinsic clearance of cyclophosphamide to 4-hydroxycyclophosphamide, and among sixteen lupus nephritis patients, those with at least one loss-of-function allele had a bioactivation ratio roughly five-fold lower than those without, a difference that reached statistical significance despite the small sample [13]. A subsequent synthesis by the same research group across multiple cohorts, comprising 567 non-Hodgkin lymphoma patients, 189 patients with systemic lupus erythematosus, 359 patients with acute leukemia, and 230 breast cancer patients, confirmed that CYP2C192 *genotype alone explained 23.6 percent of the variance in 4-hydroxycyclophosphamide area-under-the-curve among lupus nephritis patients, while combined CYP2C19 and CYP2B6 genotyping explained 47.9 percent, and that CYP2C192* homozygosity was associated with markedly poorer treatment response among lymphoma patients, with an odds ratio of 0.26 for achieving response [7]. Population pharmacokinetic modeling in HSCT recipients has corroborated that genetic covariates measurably affect cyclophosphamide clearance, although in a cohort of twenty-one patients genotyped across CYP2B6, GSTA1, GSTM1, GSTP1, GSTT1, CYP2C19, CYP3A5, ABCB1, and ABCC2, an ABCC2 transporter polymorphism, rather than a cytochrome P450 variant, emerged as the strongest single predictor, reducing non-induced clearance by approximately fifty-one percent in heterozygous carriers, underscoring that transporter genetics can rival or exceed metabolic enzyme genetics in some populations [14].

Bioactivation ratio (4-hydroxycyclophosphamide:cyclophosphamide) and hepatic intrinsic clearance in patients and human liver microsomes carrying at least one CYP2C19 or CYP2B6 loss-of-function allele versus those without, illustrating the combined genotype effect on cyclophosphamide activation (Helsby et al., 2010).



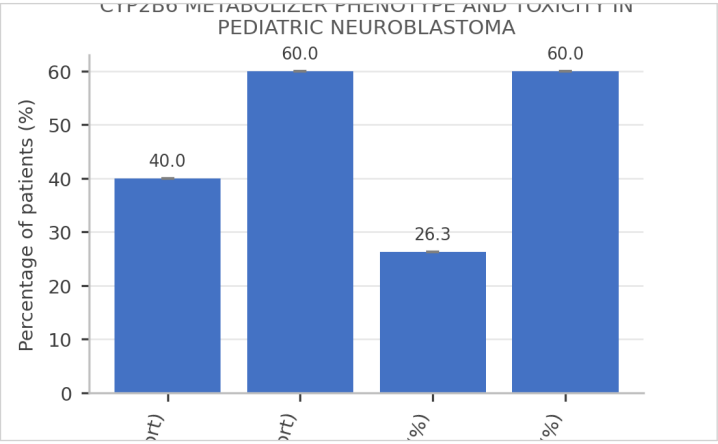
Not every pharmacokinetic study has replicated these associations, however, and this inconsistency is itself informative. In a cohort of pediatric cancer patients profiled across 372 single nucleotide polymorphisms spanning fourteen drug-metabolizing genes, no genetic variant survived correction for multiple testing as a significant predictor of cyclophosphamide clearance or 4-hydroxycyclophosphamide formation, with clinical variables, patient age and chemotherapy regimen, instead emerging as the dominant covariates [15]. Helsby and colleagues have proposed that phenoconversion, in which comedications or disease-related inflammatory suppression of enzyme expression cause phenotype to diverge from genotype, may explain why an apparent CYP2C19 association observed at one treatment cycle in breast cancer patients became obscured by within-patient variability at a subsequent cycle in the same patients [11]. This body of largely concordant, but not universally replicated, pharmacokinetic evidence establishes CYP2B6 and CYP2C19 as biologically plausible and frequently significant, but not deterministic, single-gene predictors of cyclophosphamide bioactivation.

Genotype-Outcome Associations: Efficacy, Toxicity, and Reproductive Endpoints

Beyond pharmacokinetic exposure, a substantial literature has examined whether CYP2B6, CYP2C19, GSTA1, and ALDH1A1 genotypes predict clinically meaningful efficacy and toxicity outcomes. In node-positive breast cancer patients treated with adjuvant cyclophosphamide-based chemotherapy, Gor and colleagues genotyped eight drug-metabolizing enzyme variants in 350 women and found that carriers of at least one CYP3A4*1B variant allele had significantly worse disease-free survival, with a hazard ratio of 2.79, providing early evidence that metabolic gene variation independently predicts long-term outcome after adjuvant chemotherapy [16]. Bray and colleagues, studying a comparably sized doxorubicin-cyclophosphamide cohort, reported that CYP2B62* carriers experienced markedly reduced progression-free survival, with a hazard ratio of 4.646, and that SLC22A16 and ABCB1 transporter variants independently

modulated both dose-delay incidence and overall survival, reinforcing that transporter and metabolic enzyme genotypes act in combination rather than in isolation [17]. In a global genome-wide screening array of 250 breast cancer patients, Kalra and colleagues identified CYP2C19 G681A (the *2 allele) and the ALDH1A12 seventeen-base-pair deletion as the two variants meeting genome-wide significance for association with poor disease outcome, explicitly noting that both genes lie on the cyclophosphamide pharmacokinetic pathway [9].

Toxicity outcomes stratified by cyclophosphamide-metabolizing enzyme genotype: severe leucopenia risk by GSTA1*B carrier status in breast cancer patients (Afsar et al., 2012), and hepatotoxicity by CYP2B6 metabolizer phenotype in pediatric neuroblastoma patients (Mango et al., 2023).



Toxicity associations have proven similarly consistent for GSTA1. Afsar and colleagues found that GSTA1*B carriers had a nearly seven-fold increased risk of severe leucopenia, with an odds ratio of 6.94, and concluded that myelotoxicity tracked with detoxification enzyme genotype rather than with the rate of 4-hydroxycyclophosphamide formation itself, a mechanistically important dissociation between activation-driven efficacy and detoxification-driven safety [5]. In the setting of haploidentical HSCT with post-transplantation cyclophosphamide, Muñiz and colleagues genotyped 182 patients across forty variants in eleven cyclophosphamide metabolism genes and found that activation-pathway variants, including CYP2B65, CYP2C83, and CYP2C92*, were associated with increased grade II-IV and III-IV acute graft-versus-host disease, while detoxification-pathway deficiency variants, the GSTT1 null allele and GSTA1*B, were associated with higher rates of severe acute graft-versus-host disease, and GSTM1 null status predicted increased sinusoidal obstruction syndrome risk among myeloablative-conditioning patients [1]. In pediatric neuroblastoma, Mangó and colleagues classified fifty patients by CYP2B6 metabolizer phenotype and found that normal or rapid metabolizers experienced significantly higher rates of elevated hepatic transaminases, sixty percent versus 26.3 percent among poor or intermediate metabolizers, along with significantly more grade 3 lymphopenia and severe thrombocytopenia, directly linking faster bioactivation to greater hematologic and hepatic toxicity in children [18]. In Bangladeshi breast cancer patients receiving CEF or CAF regimens, Islam and colleagues reported that the ALDH1A1 rs13959 TT genotype was associated with a markedly higher odds of favorable treatment response, an adjusted odds ratio of 6.40, while the same genotype also carried increased risk of anemia, illustrating that the efficacy-toxicity trade-off inherent to reduced detoxification capacity operates at the level of a single, clinically genotypable variant [4]. Not all outcome domains show equally consistent genetic signal: in a cohort of twenty premenopausal women receiving doxorubicin-cyclophosphamide, Wessels and colleagues found that chemotherapy-induced amenorrhea was predicted by patient age, thirty-nine years among those with sustained amenorrhea versus thirty-three years among those who remained premenopausal, but not by any of the CYP450 polymorphisms tested, indicating that ovarian toxicity may be governed more by baseline ovarian reserve than by cyclophosphamide-metabolizing genotype [8].

Toward Genotype-Guided Dosing: Feasibility, Barriers, and Unresolved Questions

The cumulative pharmacokinetic and outcome evidence outlined above provides a biological rationale for genotype-guided cyclophosphamide dosing, yet several barriers currently prevent translation into a validated clinical algorithm comparable to existing CPIC guidelines for other chemotherapeutic agents. First, the relevant pharmacogenetic architecture is multigenic rather than monogenic: activation is shared across CYP2B6, CYP2C19, CYP3A4, and CYP3A5, while detoxification is distributed across ALDH1A1, GSTA1, and other glutathione S-transferase isoforms, and transporter genes such as ABCC2 can exert effects of comparable magnitude to the metabolic enzymes themselves, as demonstrated in the HSCT population pharmacokinetic analysis in which an ABCC2 variant, not a cytochrome P450 variant, was the dominant genetic covariate of clearance [14]. A dosing algorithm restricted to CYP2B6 or CYP2C19 alone would therefore capture only part of the relevant genetic variance, and the combined-genotype analysis showing that CYP2C19 and CYP2B6 together explain nearly forty-eight percent of 4-hydroxycyclophosphamide exposure variability, versus under a quarter for CYP2C19 alone, argues for a multigene composite score rather than a single-gene rule [7].

Second, autoinduction and phenoconversion introduce a temporal and environmental dimension that static germline genotyping cannot capture. Because cyclophosphamide bioactivation increases across sequential doses of a multi-day conditioning regimen, and because comedications can transiently suppress or induce the same enzymes, a single pre-treatment genotype may predict first-dose exposure poorly, and later-cycle exposure even less well, as shown by the attenuation of a CYP2C19 association with cyclophosphamide bioactivation between the first and third treatment cycle in the same breast cancer patients [11,10]. This suggests that genotype-guided initial dose selection may need to be paired with therapeutic drug monitoring or Bayesian dose adjustment during multi-day regimens rather than functioning as a one-time, static prescribing decision. Third, the disease-context specificity of the available evidence complicates generalization: associations identified in adult breast cancer cohorts, pediatric neuroblastoma patients, lupus nephritis patients, and haploidentical HSCT recipients do not necessarily transfer across settings, given differences in cyclophosphamide dose intensity, co-administered agents, and the underlying disease biology, and the negative pediatric candidate-gene study in which no variant survived multiple-testing correction after profiling 372 SNPs across fourteen genes is a caution against assuming that pharmacogenomic effects established in one population will automatically replicate in another [15].

Finally, the marked interethnic variation in CYP2C19 loss-of-function allele frequency, elevated in Oceanian and East Asian populations relative to European populations, means that any genotype-guided dosing algorithm developed and validated predominantly in one ancestral population risks miscalibration if

applied without local validation elsewhere, a concern that mirrors broader challenges in translating pharmacogenomic dosing guidance across diverse populations [12]. Computational and mechanistic modeling of the cyclophosphamide bioactivation pathway, which has begun to quantify the relative catalytic contributions of individual CYP isoforms at the atomic level, may eventually help refine which genetic variants are mechanistically dominant enough to warrant inclusion in a composite dosing score, but this modeling remains at an early, largely theoretical stage relative to the clinical pharmacogenetic literature [2].

Conclusion

The published pharmacogenomic literature on cyclophosphamide establishes, with substantial but incomplete consistency, that genetic variation in CYP2B6-, CYP2C19-mediated bioactivation and ALDH1A1-, GSTA1-mediated detoxification meaningfully shapes interindividual differences in 4-hydroxycyclophosphamide exposure, treatment response, and toxicity across breast cancer, pediatric oncology, lupus nephritis, and hematopoietic stem cell transplantation settings. CYP2B6 and CYP2C19 loss-of-function variants have been repeatedly linked to reduced bioactivation and, in several cohorts, to inferior treatment response, while GSTA1 and ALDH1A1 variants that impair detoxification have been consistently associated with increased hematologic and hepatic toxicity, sometimes alongside improved efficacy, reflecting a genuine pharmacological trade-off rather than a uniformly favorable or unfavorable genotype. At the same time, negative and inconsistent findings, phenoconversion, autoinduction over multi-day regimens, transporter gene contributions rivaling those of metabolic enzymes, and pronounced interethnic allele frequency differences collectively explain why no consensus genotype-guided cyclophosphamide dosing algorithm has yet been validated or adopted into clinical guidelines, in contrast to the CPIC-endorsed algorithms available for several other cytotoxic and non-cytotoxic drugs. Realizing the promise of genotype-guided cyclophosphamide dosing will likely require prospective, multigene, disease-context-specific validation studies that combine germline genotyping with therapeutic drug monitoring to address the temporal instability introduced by autoinduction and phenoconversion, an integrative approach that current single-gene, single-cohort studies have only begun to approximate.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Ausra Petraitiene conceived the review, conducted the literature search, and drafted the manuscript. Matteo Fabbri contributed to the pharmacokinetic and oncological framing and critically revised the manuscript for important intellectual content. Yana Kolev contributed genetic and pharmacogenomic context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

References

1. Muñiz P, Andrés-Zayas C, Carbonell D, Chicano M, Bailén R, Oarbeascoa G, Suárez-González J, Gómez Centurión I, Dorado N, Gallardo D, Anguita J, Kwon M, Díez-Martín JL, Martínez-Laperche C, Buño I (2022) Association between gene polymorphisms in the cyclophosphamide metabolism pathway with complications after haploidentical hematopoietic stem cell transplantation. Frontiers in Immunology, 13:1002959, DOI:10.3389/fimmu.2022.1002959.

2. Dabbish E, Scoditti S, Shehata MNI, Ritacco I (2024) Insights on cyclophosphamide metabolism and anticancer mechanism of action: A computational study. Journal of Computational Chemistry, 45(10):663-670, DOI:10.1002/jcc.27280.

3. Ekhart C, Doodeman VD, Rodenhuis S, Smits PH, Beijnen JH, Huitema ADR (2008) Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide. Pharmacogenetics and Genomics, 18(6):515-523, DOI:10.1097/FPC.0b013e3282fc9766.

4. Islam MS, Akter F, Rahman MM, Rafe MR, Aziz MA, Parvin S, Mosaddek ASM, Islam MS, Akter MW (2024) Impact of ALDH1A1 and NQO1 gene polymorphisms on the response and toxicity of chemotherapy in Bangladeshi breast cancer patients. Cancer Chemotherapy and Pharmacology, 94(4):507-516, DOI:10.1007/s00280-024-04700-5.

5. Afsar NA, Ufer M, Haenisch S, Remmler C, Mateen A, Usman A, Ahmed KZ, Ahmad HR, Cascorbi I (2012) Relationship of drug metabolizing enzyme genotype to plasma levels as well as myelotoxicity of cyclophosphamide in breast cancer patients. European Journal of Clinical Pharmacology, 68(4):389-395, DOI:10.1007/s00228-011-1134-0.

6. Nakajima M, Komagata S, Fujiki Y, Kanada Y, Ebi H, Itoh K, Mukai H, Yokoi T, Minami H (2007) Genetic polymorphisms of CYP2B6 affect the pharmacokinetics/pharmacodynamics of cyclophosphamide in Japanese cancer patients. Pharmacogenetics and Genomics, 17(6):431-445, DOI:10.1097/FPC.0b013e328045c4fb.

7. Helsby NA, Yong M, van Kan M, de Zoysa JR, Burns KE (2019) The importance of both CYP2C19 and CYP2B6 germline variations in cyclophosphamide pharmacokinetics and clinical outcomes. British Journal of Clinical Pharmacology, 85(9):1925-1934, DOI:10.1111/bcp.14031.

8. Wessels AM, Flockhart DA, Carpenter JS, Radovich M, Li L, Miller KD, Sledge GW, Storniolo AM, Otte JL, Lemler SM, Schneider BP (2011) Cytochrome P450 polymorphisms and their relationship with premature ovarian failure in

premenopausal women with breast cancer receiving doxorubicin and cyclophosphamide. The Breast Journal, 17(5):536-538, DOI:10.1111/j.1524-4741.2011.01144.x.

9. Kalra S, Kaur RP, Ludhiadch A, Shafi G, Vashista R, Kumar R, Munshi A (2018) Association of CYP2C19*2 and ALDH1A1*1/*2 variants with disease outcome in breast cancer patients: results of a global screening array. European Journal of Clinical Pharmacology, 74(10):1291-1298, DOI:10.1007/s00228-018-2505-6.

10. Huitema ADR, Mathôt RAA, Tibben MM, Rodenhuis S, Beijnen JH (2001) A mechanism-based pharmacokinetic model for the cytochrome P450 drug-drug interaction between cyclophosphamide and thiotepa and the autoinduction of cyclophosphamide. Journal of Pharmacokinetics and Pharmacodynamics, 28(3):211-230, DOI:10.1023/A:1011543508731.

11. Helsby N, Yong M, Burns K, Findlay M, Porter D (2021) Cyclophosphamide bioactivation pharmacogenetics in breast cancer patients. Cancer Chemotherapy and Pharmacology, 88(3):533-542, DOI:10.1007/s00280-021-04307-0.

12. Shubbar Q, Alchakee A, Issa KW, Adi AJ, Shorbagi AI, Saber-Ayad M (2024) From genes to drugs: CYP2C19 and pharmacogenetics in clinical practice. Frontiers in Pharmacology, 15:1326776, DOI:10.3389/fphar.2024.1326776.

13. Helsby NA, Hui CY, Goldthorpe MA, Coller JK, Soh MC, Gow PJ, de Zoysa JZ, Tingle MD (2010) The combined impact of CYP2C19 and CYP2B6 pharmacogenetics on cyclophosphamide bioactivation. British Journal of Clinical Pharmacology, 70(6):844-853, DOI:10.1111/j.1365-2125.2010.03789.x.

14. Kim IW, Yun H, Choi B, Han N, Kim MG, Park S, Oh JM (2013) Population pharmacokinetics analysis of cyclophosphamide with genetic effects in patients undergoing hematopoietic stem cell transplantation. European Journal of Clinical Pharmacology, 69(8):1543-1551, DOI:10.1007/s00228-013-1507-7.

15. Navarro SL, Pinto N, Hawkins DS, Park JR, Dilmaghani S, Rimorin C, Wurscher M, McCune JS (2024) Pharmacogenomic associations of cyclophosphamide pharmacokinetic candidate genes with 4-hydroxycyclophosphamide formation in children with cancer. Cancer Chemotherapy and Pharmacology, 94(4):627-633, DOI:10.1007/s00280-024-04703-2.

16. Gor PP, Su HI, Gray RJ, Gimotty PA, Horn M, Aplenc R, Vaughan WP, Tallman MS, Rebbeck TR, DeMichele A (2010) Cyclophosphamide-metabolizing enzyme polymorphisms and survival outcomes after adjuvant chemotherapy for node-positive breast cancer: a retrospective cohort study. Breast Cancer Research, 12(3):R26, DOI:10.1186/bcr2570.

17. Bray J, Sludden J, Griffin MJ, Cole M, Verrill M, Jamieson D, Boddy AV (2010) Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. British Journal of Cancer, 102(6):1003-1009, DOI:10.1038/sj.bjc.6605587.

18. Mangó K, Fekete F, Kiss ÁF, Erdős R, Fekete JT, Bűdi T, Bruckner E, Garami M, Micsik T, Monostory K (2023) Association between CYP2B6 genetic variability and cyclophosphamide therapy in pediatric patients with neuroblastoma. Scientific Reports, 13:11770, DOI:10.1038/s41598-023-38983-0.