Systematic Review of Pharmacogenetics of ABC and SLC Transporter Genes in Acute Myeloid Leukemia

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Abstract: Antineoplastic uptake by blast cells in acute myeloid leukemia (AML) could be influenced by influx and efflux transporters, especially solute carriers (SLCs) and ATP-binding cassette family (ABC) pumps. Genetic variability in SLC and ABC could produce interindividual differences in clinical outcomes. A systematic review was performed to evaluate the influence of SLC and ABC polymorphisms and their combinations on efficacy and safety in AML cohorts. Anthracycline intake was especially influenced by SLCO1B1 polymorphisms, associated with lower hepatic uptake, showing higher survival rates and toxicity in AML studies. The variant alleles of ABCB1 were related to anthracycline intracellular accumulation, increasing complete remission, survival and toxicity. Similar findings have been suggested with ABC1 and ABCG2 polymorphisms. Polymorphisms of SLC29A1, responsible for cytarabine uptake, demonstrated significant associations with survival and response in Asian populations. Promising results were observed with SLC and ABC combinations regarding anthracycline toxicities. Knowledge of the role of transporter pharmacogenetics could explain the differences observed in drug disposition in the blast. Further studies including novel targeted therapies should be performed to determine the influence of genetic variability to individualize chemotherapy schemes.

Keywords: SLCO1B1; ABCB1; SLC29A1; ABCG2; ABCC1; polymorphism; anthracyclines; cytarabine; acute myeloid leukemia

1. Introduction

Acute myeloid leukemia (AML) is a clinically and biologically heterogeneous hematologic malignant disease characterized by an excess of blast cells in bone marrow and blood. Approximately 60–80% of young AML patients achieve complete remission (CR) using conventional 3 + 7 schedules of anthracyclines and cytarabine, which might be followed by an allogeneic hematopoietic stem cell transplant (allo-HSCT) to prevent relapse [1,2]. Unfortunately, half of these patients finally relapsed or died from different causes, including: low efficacy eliminating the minimal residual disease, severe toxicity of chemotherapy, refractory disease. This interindividual variability of outcomes between AML patients could be related to their genetic variability [3,4].

Drug uptake by blast cells can be affected by different transporters, including influx and efflux transporters, especially solute carriers (SLCs) and ATP-binding cassette family (ABC) pumps, respectively [3,4]. Previous pharmacogenetic studies have suggested that single nucleotide polymorphisms (SNPs) of SLC and ABC transporters may play a promising role in drug exposure and have been associated with clinical response and toxicity [3–7]. However, the findings and the interpretation of these individual studies...
appear contradictory and inconclusive. Furthermore, for new targeted therapies, potential drug–drug interactions with P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP) were tested in preclinical studies, but the influence of SNPs in these transporters is unknown in these new therapies. We performed a systematic review of all the studies that have analyzed polymorphisms of membrane transporters in AML patients.

2. Materials and Methods

Search Strategy and Selection of Studies

A systematic search was performed following the PRISMA guidelines by two independent reviewers (JEMV and ASA) [8]. Pubmed, EMBASE, the Cochrane Central Register, the Web of Science and the Database of Abstracts of Reviews of Effects (DARE) databases were searched without restrictions. In addition, the reference lists of important studies and reviews were hand searched. The reference lists of relevant reviews and studies were manually searched. The last literature search was conducted on 26 January 2022. This systematic review was included in the PROSPERO registry (ID 314292).

Similar keywords were used in different databases: (“ATP-binding cassette transporters” [MeSH Terms] or “organic anion transporters” [MeSH] or “organic cation transport proteins” [MeSH]) and “acute myeloid leukemia” [MeSH].

Studies that fulfilled the following criteria were included: (1) studies based on clinical data in AML patients (excluding preclinical and in vitro studies); (2) AML studies analyzing the associations between ABC and/or SLC polymorphisms and clinical response to chemotherapy; and (3) AML studies analyzing the impact on safety of ABC and/or SLC polymorphisms.

3. Results

Our systematic search obtained 569 citations from databases and journals and 21 records were identified through other sources (Figure 1). Of the 44 citations selected for full reading, 37 fulfilled the inclusion criteria and were included. The agreement in the study selection between the reviewers was excellent (kappa = 0.97).

Figure 1. Summary of evidence search and selection.

3.1. Influx Transporters: SLC Family

The intake by blast cells and other tissues of the antineoplastics employed in AML therapy and other xenobiotics is mediated by SLC transporters, a family that includes more
than 400 transporters. Different SLC transporters have been related to anthracycline uptake, especially the organic anion transporter polypeptide-1B1 (OATP1B1, encoded by SLCO1B1) and the organic cation transporter SLC22A16 (Figure 2). However, cytarabine is mainly transported by human equilibrative nucleoside transporter (hENT1 and hENT2, encoded by the SLC29A1 and SCL29A2 genes; Figure 2), and in lower proportions by the human concentrative nucleoside transporters (hCNT3 encoded by the SLC28A3 gene).

Figure 2. Key candidate genes involved in drug transport in acute myeloid leukemia.

The OATP1B1 (SLCO1B1) is predominantly expressed in the liver and is involved in the hepatic uptake and plasma clearance of several organic anionic compounds, including anthracyclines and other drugs such as statins [9–12]. The most relevant SLCO1B1 polymorphisms are 521T>C (rs4149056), 388A>G (rs2306283) and 597C>T (rs2291075), which are partially in linkage disequilibrium. The minor allele of rs4149056 has been consistently associated with a lower hepatic uptake and higher drug circulating concentrations, increasing the plasma levels and the risk of toxicity in tissues [10,11]. In AML studies (Table 1), the variant allele of SLCO1B1 rs4149056 was associated with a higher liver toxicity in adult patients [5] and higher overall survival (OS) in AML children [13]. In a recent study, the wild-type TT genotype of this SNP was related to a higher induction death, probably associated with a higher idarubicin uptake in tissues and therefore a higher potential toxicity [14]. The previous study in AML pediatric patients also obtained a higher OS and event-free survival (EFS) in carriers of the variant allele of the SLCO1B1 polymorphism (rs2291075), as well as those of the SLCO1B1 haplotype *1A/*1A,*1B/*1B (rs2291075, rs4149056 and rs2306283) [13].

SLC22A12 encodes a solute carrier that is mainly expressed in kidney and other tissues and is involved in urate–anion exchange [15]. Moreover, it is associated with the transport of different drugs, especially uricosurics (allopurinol and oxypurinol). The wild-type homozygote of SLC22A12 rs11231825 showed a higher infusion-related reactions after gemtuzumab ozogamicin administration (Table 1) [5]. An association between the wild-
type genotypes of different SLC22A12, SLC25A37 and SLC28A3 polymorphisms showed a lower disease-free survival (DFS), although these associations were lost after the correction for multiple testing (Table 1) [16].

SLC22A16 encodes an organic cation transporter of L-carnitine, a metabolism cofactor related to different disease states. This carrier also imports several drugs, including anthracyclines. This transporter is constitutively expressed in the brain and kidney. SLC22A16 is over-expressed in AML and is related to the growth and viability of the blast cells, providing a potential target for future AML therapies [17]. In breast cancer cohorts, variant alleles of SLC22A16 (rs714368) were found to be related to higher exposure levels of doxorubicin and doxorubicinol [6] and dose delays by anthracycline toxicities (lower with rs714368, rs6907567, rs723685 and higher with rs12210538) [7]. In a recent AML study, associations were not observed between SLC22A16 rs12210538 and rs714368 and response or safety outcomes (Table 1) [14].

The concentrative nucleoside transporter hCNT1 encoded by the SLC28A1 gene has a substrate specificity for physiological pyrimidine nucleosides. Besides this function, hCNT1 has been implicated in tumor suppression. Various SLC28A1 SNPs were analyzed in several AML studies [18–20] (Table 1). Carriers of the SLC28A1 rs2242046 polymorphism showed a higher neutropenia [19], whereas studies with SLC28A1 rs2290272 [18] and SLC28A1 rs8025045 [20] did not find any clinical association. SLC28A2 encodes a sodium-dependent selective transporter of purines expressed in the kidney and other tissues. Only a pediatric AML study found a lower OS and EFS with the wild-type genotype of SLC28A2 rs10519020 [13].

hCNT3 (SLC28A3 gene) is a sodium-dependent pyrimidine and purine nucleoside carrier expressed in the pancreas, trachea, bone marrow and mammary glands. hCNT3 is a minor cytarabine transporter compared to hENT1, and this carrier has been associated with the uptake of different anthracyclines [21]. In four pediatric cancer cohorts, the variant alleles of SLC28A3 rs7853758 and rs885004 were correlated with cardiotoxicity associated with anthracyclines (doxorubicin and daunorubicin) [22–25], whereas this finding with SLC28A3 rs7853758 was not reproduced in cohorts of breast cancer [26,27] or B-cell lymphoma [28]. SLC28A3 rs7853758 and rs885004 SNPs are in high linkage disequilibrium and have been related to lower expression in different cell lines [29,30]. Only one study in AML patients has reported an association of SLC28A3 rs11140500 with a lower DFS, but the significance disappeared after Bonferroni correction (Table 1) [16].

hENT1 (encoded by the SLC29A1 gene) is responsible for up to 80% of cytarabine influx in blast cells. Schemes with high doses of cytarabine (2–3 g/m² daily), used in consolidation or intensification therapy, can saturate the pump-mediated transport of hENT1 with concentrations >10 µmol/L and produce free diffusion into the cell [31,32]. Nevertheless, intracellular cytarabine concentrations obtained with induction therapy (200 mg/m²) are mediated by hENT1 [33]. Moreover, the intracellular influx is strongly correlated with the abundance of hENT1 in cell surface [34], so the bioavailability and clinical response depend on hENT1 expression [35]. In addition, SLC29A1 expression can be affected by hypoxia inducible factor 1 (Hif-1) at the promoter or by the transcription factor peroxisome proliferator activated receptorα (PPARα) [36,37]. In AML, patients with a low SLC29A1 mRNA expression had a significantly shorter DFS and OS in an adult cohort [38], but this had no influence in a pediatric AML cohort [39].

Two nonsynonymous and four synonymous polymorphisms were identified in a functional study of SLC29A1, but no influence in cytarabine uptake was measured [40]. In contrast, the haplotype of three SLC29A1 polymorphisms (−1345C>G, −1050G>A and 706G>C) was correlated with higher mRNA expression [41]. Another study showed only a modest elevation in hENT1 gene expression with the variant −706G>C, but no influence on cytarabine toxicity in normal blood cells [42]. The minor alleles of SLC29A1 polymorphisms only reach relevant frequencies in Asian populations, as is reflected in AML studies (Table 1). The variant A allele SLC29A1 rs3734703 was associated with a lower OS and RFS alone [43] or combined with TYMS rs2612100 [44], but a higher CR was related
to the A allele [20] and CC + AA genotypes [43]. The SLC29A1 rs9394992 polymorphism was related to a lower CR [43], OS, DFS and mRNA expression, and a higher relapse rate (RR) [45], but no influence was found in another cohort [46]. Similarly, the variant allele of SLC29A1 rs324148 (alone or in combination rs9394992) was associated with a lower OS, DFS and mRNA expression, and a higher RR [45], as well as a higher CR haplotype ht3 with rs734703, rs9394992, rs693955, rs507964 and rs747199 but had no effect alone [43]. On the other hand, the SLC29A1 rs693955 polymorphism was correlated to a lower time to relapse and neutropenia recovery [4].

3.2. Efflux Transporters: ABC Family

The ABC family of transporters includes several efflux pumps involved in the active efflux of drugs and xenobiotics from inside the cells with a potential increase in drug resistance [47]. The effect of these pumps is well-known in anthracycline disposition in blast cells and tissues, highlighting ABCB1, ABCC1, ABCC3 and ABCG2 (Figure 2) [47,48]. In addition, cytarabine uptake is influenced by two members of the “multidrug resistance-associated protein” (MRP) family, MRP7 and MRP8 (encoded by ABCC10 and ABCC11 genes), which have been related to deoxynucleotide efflux (Figure 2) [49,50].

The P-glycoprotein (P-gp), encoded by the ABCB1 gene, is the most studied efflux pump of the ABC family. The pharmacogenetics of ABCB1 have been widely analyzed in AML patients (Table 2), especially ABCB1 3435C>T (rs1045642), 2677G>A/T (rs2032582) and 1236C>T (rs1128503) polymorphisms [13,16,19,20,51–69]. An in vitro study associated the P-gp expression with a lower intracellular daunorubicin accumulation [70]. The pharmacokinetics of daunorubicin and its metabolite daunorubicinol were not affected by ABCB1 polymorphisms, nor was mRNA expression in an Indian AML cohort [69]. However, previous studies in breast cancer have shown a higher doxorubicin clearance and lower peak levels of doxorubicinol with the wild-type haplotype of ABCB1 [47].

Lower pump function was related to the variant alleles of ABCB1, favoring anthracycline intracellular accumulation with a higher potential efficacy and toxicity [61,71,72], but some studies did not reproduce this effect [51,54,58]. Following this hypothesis, better responses (higher CR and survival rates) has been reported in AML cohorts with different ABCB1 polymorphisms [51,57,59,61,63,65–68], whereas in other studies, these SNPs showed no influence or a worse response [20,53–56,62,64] (Table 2). This finding of a higher CR and OS with variant alleles of ABCB1 3435C>T, 2677G>A/T and 1236C>T was reproduced in two meta-analyses [73,74]. The study of Rafiee et al. showed an association between three ABCB1 SNPs and a higher EFS and DFS and a lower relapse rate on gemtuzumab ozogamicin, highlighting the role of P-gp in calicheamicin efflux [64].

The toxicity of anthracyclines has only been evaluated in four AML studies, showing no associations in two studies [54,56] and relevant anthracycline related-toxicities in two studies [60,62]. He et al. found higher nausea and vomiting grades (3/4) with wild-type genotypes of ABCB1 3435C>T and 2677G>A/T (alone and in haplotype) in an Asian cohort [60]. On the other hand, in a Caucasian cohort, the variant alleles of ABCB1 3435C>T, 2677G>A/T and 1236C>T and their haplotypes were associated with higher organ toxicities (renal, hepatic and neutropenia), as well as with higher induction death [62]. In other malignancies, ABCB1 SNPs were correlated with higher cardiotoxicity [22,23,75,76], but this was not reproduced in these AML studies [54,56,60,62], nor in a large study analyzing the potential correlation between ABCB1 polymorphisms and the left ventricular ejection fraction (LVEF) [77].
| SNP     | Study                  | n   | Age (Range) | Ethnicity (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                  |
|---------|------------------------|-----|-------------|---------------------|-----|----------------|---------------------|------------------------------------|
| **SLCO1B1** |                        |     |             |                     |     |                |                     |                                    |
| T521C   | Iacobucci et al., 2012 [5] | 94  | 51 (19–65)  | Caucasian (Italy)   | Yes | De novo (80.9%) Secondary (19.1%) | Ara C + IDA + FLUDA + GO | - CR: no influence  |
|         |                        |     |             |                     |     |                |                     | - Toxicity: CC/CT liver toxicity    |
|         | Drenberg et al., 2016 [13] | 164 | 9.1 (0–21)  | White (70%) Black (20%) Others (10%) | Yes | De novo | Ara C + DAUNO + ETOP + MIT | - OS: TT ↓OS (p: 0.05) |
|         |                        |     |             |                     |     |                |                     | - EFS: no influence               |
|         |                        |     |             |                     |     |                |                     | - Toxicity: no influence           |
|         |                        |     |             |                     |     |                |                     | - Haplotype *1A/*1A,*1B/*1B (rs2291075, rs4149056 & rs2306283): ↓OS y ↓EFS |
|         | Megías-Vericat et al., 2021 [14] | 225 | 52.5 (16–78) | Caucasian           | Yes | De novo | Ara C + IDA | - CR: no influence |
|         |                        |     |             |                     |     |                |                     | - Induction death: TT ↑induction death (p: 0.049) |
|         |                        |     |             |                     |     |                |                     | - Toxicity: no influence           |
| 597C>T  | Drenberg et al., 2016 [13] | 164 | 9.1 (0–21)  | White (70%) Black (20%) Others (10%) | Yes | De novo | Ara C + DAUNO + ETOP + MIT | - OS: CC ↓OS (p: 0.012) |
|         |                        |     |             |                     |     |                |                     | - EFS: CC ↓EFS (p: 0.006)          |
|         |                        |     |             |                     |     |                |                     | - Toxicity: no influence           |
|         |                        |     |             |                     |     |                |                     | - Haplotype *1A/*1A,*1B/*1B (rs2291075, rs4149056 & rs2306283): ↓OS y ↓EFS |
| 388A>G  | Drenberg et al., 2016 [13] | 164 | 9.1 (0–21)  | White (70%) Black (20%) Others (10%) | Yes | De novo | Ara C + DAUNO + ETOP + MIT | - OS: no influence |
|         |                        |     |             |                     |     |                |                     | - EFS: no influence               |
|         |                        |     |             |                     |     |                |                     | - Toxicity: no influence           |
|         |                        |     |             |                     |     |                |                     | - Haplotype *1A/*1A,*1B/*1B (rs2291075, rs4149056 & rs2306283): ↓OS y ↓EFS |
| **SLC22A12** |                  |     |             |                     |     |                |                     |                                    |
| T1246C  | Iacobucci et al., 2012 [5] | 94  | 51 (19–65)  | Caucasian (Italy)   | Yes | De novo (80.9%) Secondary (19.1%) | Ara C + IDA + FLUDA + GO | - CR: no influence  |
|         |                        |     |             |                     |     |                |                     | - Toxicity: TT/CT ↑fever reaction (associated with GO administration) |
| rs528211 | Yee et al., 2013 [16] | 154 | NR          | Caucasian (Europe)  | NR  | NR            | Ara C + ETOP + BUSUL (pre-TX) | - DFS (pre-TX): GG ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
| (G>A)   |                        |     |             |                     |     |                |                     |                                    |
| rs2360872| Yee et al., 2013 [16] | 154 | NR          | Caucasian (Europe)  | NR  | NR            | Ara C + ETOP + BUSUL (pre-TX) | - DFS (pre-TX): CC ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
Table 1. Cont.

| SNP        | Study                          | n    | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                        |
|------------|--------------------------------|------|-------------|------------------|-----|-----------------|----------------------|------------------------------------------|
| rs505802   | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): AA ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
| rs524023   | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): GG ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
| rs9734313  | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): TT ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
| rs11231825 | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): CC ↓DFS (p: 0.0048). No influence in non-Caucasian cohort |
| rs1160370  | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): AA ↓DFS (p: 0.005). No influence in non-Caucasian cohort |
| rs893006   | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): TT ↓DFS (p: 0.0055). No influence in non-Caucasian cohort |

**SLC22A16**

| SNP        | Study                          | n    | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                        |
|------------|--------------------------------|------|-------------|------------------|-----|-----------------|----------------------|------------------------------------------|
| rs12210538 | Megías-Vericat et al., 2021 [14] | 225  | 52.5 (16–78) | Caucasian (Spain) | Yes | De novo         | Ara C + IDA           | CR and induction death: no influence Toxicity: no influence |
| rs714368   | Megías-Vericat et al., 2021 [14] | 225  | 52.5 (16–78) | Caucasian (Spain) | Yes | De novo         | Ara C + IDA           | CR and induction death: no influence Toxicity: no influence |

**SLC25A37**

| SNP        | Study                          | n    | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                        |
|------------|--------------------------------|------|-------------|------------------|-----|-----------------|----------------------|------------------------------------------|
| rs7818607  | Yee et al., 2013 [16] ²        | 154  | NR          | Caucasian (Europe) | NR  | NR              | Ara C + ETOP + BUSUL (pre-TX) | DFS (preTX): AA ↑DFS (p: 0.0057). No influence in non-Caucasian cohort |
| SNP       | Study                  | n  | Age (Range) | Ethnicity       | HWE | LMA Status (%) | Chemotherapy Scheme                  | Clinical Outcomes                                                                 |
|-----------|------------------------|----|-------------|-----------------|-----|----------------|---------------------------------------|-----------------------------------------------------------------------------------|
| rs8534    | Yee et al., 2013 [16]  | 154| NR          | Caucasian (Europe) | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX)         | DFS (preTX): TT ↓ DFS (p: 0.0067), No influence in non-Caucasian cohort            |
| SNPs      |                        |    |             |                 |     |                |                                       |                                                                                   |
| rs2290272 | Müller et al., 2008 [18]| 139| 46.3 (15–86) | Jews (61.2%) Arab (38.8%) | Yes | De novo        | Ara C + ANT ± FLUDA ± MIT            | OS (TX censured): no influence                                                    |
| rs2242046 | Seeringer et al., 2009 [19]| 322| <60         | Caucasian (Germany) | NR  | NR (normal cytogenetic status) | Ara C + IDA + ETOP                  | -                                                                                  |
| rs8025045 | Cao et al., 2017 [20]  | 206| 67.2 (22–98) | Asian (China)    | Yes | De novo        | Ara C + ANT                          | - CR: no influence - OS: no influence - RFS: no influence - Toxicity: no influence |
| rs10519020| Drenberg et al., 2016 [13] | 164| 9.1 (0–21)  | White (70%) Black (20%) Others (10%) | Yes | De novo        | Ara C + DAUNO + ETOP + MIT           | OS: GG ↓ OS (p: 0.002) - EFS: GG ↓ EFS (p: 0.001)                                  |
| rs11149500| Yee et al., 2013 [16]  | 154| NR          | Caucasian (Europe) | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX)         | DFS (preTX): TT ↓ DFS (p: 0.00018), No influence in non-Caucasian cohort           |
| rs3734703 | Kim et al., 2013 [44]  | 97 | 50 (16–76)  | Asian (South Korea) | Yes | De novo        | Ara C + IDA                          | - CR, OS, RFS: no influence individually - OS, RFS: AA/AC combined with TYMS AA genotype (rs2612100) ≫ OS and RFS (OS loses statistically significant after multivariable analysis) - Toxicity (hematologic): no influence |

Table 1. Cont.
| SNP          | Study                  | n  | Age (Range) | Ethnicity (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                      |
|--------------|------------------------|----|-------------|---------------------|-----|----------------|---------------------|--------------------------------------------------------|
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| RR: CC ↓RR (p: 0.0004)                                  |
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| OS: CC ↓OS against CT (p: 0.02) and TT (p: 0.005)       |
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| mRNA expression: CC ↑expression (p < 0.01)              |
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| SNP-SNP interaction: CC+CT/TT (rs9394992) ↓OS (p < 0.001) and ↓DFS (p: 0.005) |
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| SNP-SNP interaction: CC+CT/TT (rs324148) ↓OS (p < 0.001) and ↓DFS (p: 0.005) |
| T>C          | Wan et al., 2014 [45]  | 100| 43 (17–76)  | Asian (China)       | Yes | De novo        | Ara C + DAUNO or IDA| SNP-SNP interaction: CC+CT/TT (rs324148) ↓OS (p < 0.001) and ↓DFS (p: 0.005) |

Table 1. Cont.
| SNP          | Study                   | n     | Age (Range) | Ethnia (Country) | HWE  | LMA Status (%) | Chemotherapy Scheme                  | Clinical Outcomes                                                                 |
|-------------|-------------------------|-------|-------------|------------------|------|----------------|---------------------------------------|-----------------------------------------------------------------------------------|
|             | Kim et al., 2016 [43]   | 103   | 50.4 (16–76) | Asian (South Korea) | Yes  | De novo        | Ara C + IDA                           | CR: no influence, ↑CR haplotype ht3 (p: 0.01)                                    |
| A>C         | Amaki et al., 2015 [46] | 39    | 54 (23–71)  | Asian (Japan)    | Yes  | De novo        | Ara C + IDA or DAUNO (consolidation: Ara C high doses) | OS: no influence. TTR: CC ↓ TTR (p: 0.00261; 0.0096 in multivariable analysis) Hematologic toxicity: CC ↓ neutropenia duration |
| rs693955    |                         |       |             |                  |      |                |                                       |                                                                                   |
| rs507964    | Kim et al., 2016 [43]   | 103   | 50.4 (16–76) | Asian (South Korea) | Yes  | De novo        | Ara C + IDA                           | CR: no influence, ↑CR haplotype ht3 (p: 0.01)                                    |
| (A>C)       |                         |       |             |                  |      |                |                                       |                                                                                   |
| rs747199    | Kim et al., 2016 [43]   | 103   | 50.4 (16–76) | Asian (South Korea) | Yes  | De novo        | Ara C + IDA                           | CR: G allele ↑CR (p: 0.02; p Bonferroni:NS) and haplotype ht3 (p: 0.01)           |
| (C>G)       |                         |       |             |                  |      |                |                                       |                                                                                   |

**Abbreviations:** AMSA: amsacrine; ANT: anthracycline; BUSUL: busulfan; CR: complete remission; DAUNO: daunorubicin; DFS: disease-free survival; EFS: event-free survival; ETOP: etoposide; FLUDA: fludarabine; GO: gemtuzumab–ozogamicin; HWE: Hardy–Weinberg equilibrium; IDA: idarubicin; MIT: mitoxantrone; NR: not reported; OS: overall survival; RFS: relapse-free survival; RR: rate of relapse; TX: hematologic transplant. ¹—This study [13] analyzed 1936 SNPs of 225 genes with a multi-SNP-based approach (including ABC and SLC transporters). Only SNPs with significant results were cited. ²—This study [16] analyzed 1659 SNPs of 42 genes with multi-SNP based approach. Only SNPs with significant results were cited. ³—This study [19] included SNPs of genes potentially involved in the response to Ara C (hCNT1, hENT1, hENT2, DCK, CDA), but only specified the SNPs with significant effect. ⁴—This study [44] included 139 SNPs of 10 genes potentially involved in the response to Ara C, but only specified the SNPs with significant effect.
ABCB11 encodes a canalicular transporter of bile salts also called the “bile salt export pump” (BSEP) which has been associated with the efflux of some anticancer drugs in liver cells. The ABCB11 rs4668115 and ABCB4 rs2302387 polymorphisms reduced transporter expression and were found to be related to ≥grade 3 transaminitis after anthracycline infusion (mithramycin) in patients with refractory thoracic malignancies [78]. The wild-type genotype of ABCB11 rs4668115 was correlated with a lower OS and EFS in AML patients (Table 2) [13].

ABCC1 encodes the MRP1 pump, which mediates the export of organic anions and drugs from the cytoplasm, including methotrexate, antivirals and anthracyclines. The function of this pump confers resistance to anticancer drugs by decreasing their accumulation in cells and by mediating ATP- and GSH-dependent drug export [79]. Pharmacokinetic in vitro studies have shown decreased transport and higher maximum velocity (Vmax) of doxorubicin disposition with ABCC1 (rs60782127) [80], whereas MRP expression reduced the intracellular daunorubicin accumulation [70]. Previous studies in other cancers have associated ABCC1 (rs3743527, rs246221, rs4148350) with higher cardiotoxicity [22,23,27,81]. A small cohort performed in an Arab population correlated the expression of 4 ABCC1 SNPs with a lower CR, drug sensitivity and relapsed/refractory disease in acute leukemia (Table 2) [82]. Subsequently, several AML studies analyzed the role of different ABCC1 genotypes in clinical outcomes and safety (Table 2) [20,56,62,83]. Despite the fact that the association between cardiotoxicity and ABCC1 polymorphisms was not reproduced in AML [20,56,62,83], ABCC1 rs4148350 was related to hepatotoxicity [62], ABCC1 rs212090 with gastrointestinal toxicity and rs212091 and rs3743527 with myelosuppression [20]. In addition, the ABCC1 rs212090 and rs3743527 variant alleles showed lower survival rates, whereas ABCC1 rs129081 increased OS and DFS [83].

ABCC2 expresses MPR2, an export pump localized to the apical membrane of polarized cells, especially those hepatocytes with functions in biliary transport. This protein appears to contribute to the drug resistance of different anticancer drugs including anthracyclines [84]. Polymorphisms of ABCC2 have been correlated with anthracycline toxicities in other malignancies: cardiotoxicity in non-Hodgkin lymphoma (rs45511401) [26], in survivors of HSCT (rs8187710) [85] and in pediatric cancer (rs4148350) [22], febrile neutropenia in breast cancer (rs4148350) [27] and leucopenia in osteosarcoma (17222723) [86]. In AML patients, only one cohort has analyzed ABCC2 rs8187710, without any significant influence in response or toxicity [62].

ABCC3 encodes a protein that may play a role in biliary transport and the intestinal excretion of organic anions, which is also related to drug efflux. The expression of ABCC3 was found to be significantly higher in AML patients resistant to daunorubicin [87]. Clinical studies in AML cohorts corroborated this finding with ABCC3 polymorphisms (Table 2) [16,18,88]. A lower DFS was reported with variant alleles of ABCC3 polymorphisms (rs4148405, rs1989983, rs2301835, rs8079740), whereas other ABCC3 (rs2277624, rs757420) SNPs showed a higher DFS [16]. A similarly higher OS was observed with the variant allele of ABCC3, rs4793665 [18]. A recent cohort reproduced the previous findings of lower OS rates with the minor allele of ABCC3, rs4148405 [88].

The ABCG2 gene expresses the “breast cancer resistant protein” (BCRP), a well-known ABC pump responsible for anthracycline efflux [91]. BCRP is localized in the cell membranes of epithelial cells of the small intestine, liver, kidney, brain and placenta [92]. In AML, an overexpression of ABCG2 was observed in 33% of blast cells and this BCRP expression correlated with a worse prognosis and lower OS [93–96]. The two most common ABCG2 SNPs are rs2231137 and rs2231142, and the minor alleles of these SNPs are related
to a reduced level of BCRP expression [92]. No influence in anthracycline pharmacokinetics was reported with ABCG2 in an AML cohort with daunorubicin (rs2231137, rs2231142, rs769188) [69] or a breast cancer cohort with doxorubicin (rs2231142) [47]. Several studies have described the impact of ABCG2 genotypes in AML (Table 2) [18,56,62,97,98]. Contradictory results were observed with ABCG2 rs2231137, showing a lower OS and lower risk of toxicities ≥ grade three with the GG wild-type genotype in a Caucasian cohort [56], but a higher OS and DFS in a mixed AML/ALL Asian cohort [97] and no influence in a Caucasian cohort [62]. On the other hand, three different cohorts reproduced an increase in OS in wild-type ABCG2 rs2231142 carriers [56,97,98] and cardiac and lung toxicities were associated with the variant allele in another study [62]. Similar OS and DFS increases were obtained with the wild-type genotype of ABCG2 rs2231149, as well as with its haplotype with the ABCG2 rs2231137 and rs2231142 polymorphisms [97]. No effect in LVEF was observed with 16 different ABCG2 polymorphisms in a large study [77].

Table 2. Characteristics of the studies included in the systematic review for polymorphisms of the ABC transporter family.

| SNP          | Study                  | n   | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                  |
|--------------|------------------------|-----|-------------|------------------|-----|----------------|---------------------|-----------------------------------|
| ABCB1        |                        |     |             |                  |     |                |                     |                                   |
| C3435T       | Illmer et al., 2002 [51]| 405 | 53 (17–78)  | Caucasian (Germany) | Yes | De novo        | Ara C + MIT + ETOP + AMSA | - CR: no influence.               |
|              |                        |     |             |                  |     |                |                     | - OS and DFS at 4 years (TX censured): CC ↓ OS (CC vs. CT p < 0.01, CC vs. CT/TT p: 0.05). |
|              |                        |     |             |                  |     |                |                     | - Haplotype with G2677T/A and C1236T: wild-type ↓ OS and DFS at 4 years. |
|              |                        |     |             |                  |     |                |                     | - mRNA expression: CC ↓ expression (p < 0.05) |
| Kaya et al., 2005 [52] | 28 | 36 (20–64) | Arabs (Turkey) | NR | NR | Ara C + ANT | - Drug sensitive/resistant: no differences (mixed with ALL cohort) |
| Kim DH et al., 2006 [53] | 81 | 39 (15–72) | Asian (South Korea) | Yes | De novo | Ara C + IDA | - CR: CC ↑ CR (p: 0.05) |
|              |                        |     |             |                  |     |                |                     | - OS at 3 years (TX censured): no influence. |
|              |                        |     |             |                  |     |                |                     | - EFS at 3 years (TX censured): CC ↑ EFS (p: 0.01) |
|              |                        |     |             |                  |     |                |                     | - Haplotype with G2677T/A: wild-type ↑ CR and EFS at 3 years. |
|              |                        |     |             |                  |     |                |                     | - mRNA expression: CC ↓ expression (p: 0.03) |
| Van der Holt et al., 2006 [54] | 150 | 67 (60–85) | Caucasian (Netherlands) | No | De novo: 79Secondary: 21 | Ara C + DAUNO | - CR, OS, EFS, DFS at 5 years: no influence. |
|              |                        |     |             |                  |     |                |                     | - Expression and activity of P-gp: no influence |
| Hur et al., 2008 [55] | 200 | 44 (NR) | Asian (South Korea) | Yes | De novo | Ara C + ANT | - CR, OS, RFS and EFS at 5 years: no influence |
| Hampras et al., 2010 [56] | 261 | 61.5 (20–65) | Caucasian (86%) Others (14%) (USA) | Yes | De novo: 79Secondary: 25 | Ara C + ANT | - OS (TX censured): no influence |
|              |                        |     |             |                  |     |                |                     | - Toxicity: no influence |
Table 2. Cont.

| SNP                  | Study                        | n     | Age (Range) | Ethnia (Country) | HWE   | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                                                 |
|----------------------|------------------------------|-------|-------------|------------------|-------|----------------|---------------------|------------------------------------------------------------------------------------|
| Green et al., 2012 [57] | 100                          | 63    | 20–85       | Caucasian (Europe) | Yes   | De novo (normal karyotype) | Ara C + ANT or MIT +/- or Others | - OS at 4 years (TX censured): no influence                                       |
| Scheiner et al., 2012 [58] ² | 109 (44)                      | 34    | <1–86       | Others: White (69.7%) Non-white (30.3%) | No    | De novo: 72.5Secondary: 18.3 | Ara C + IDA | - OS at 5 years: no influence. EFS at 5 years: CT ↑EFS (p: 0.001) - Expression and activity of P-gp: no influence |
| Falk et al., 2014 [59] ³ | 201                          | 59    | 18–85       | Caucasian (Sweden) | Yes   | De novo (normal karyotype) | Ara C + DAUNO or IDA +/- ETOP +/- or Others | - CR, OS, EFS: no influence (similar results in FLT3 wild-type subgroup). |
| He et al., 2014 [60]     | 215                          | 43.6  | 14–57       | Asian (China)    | Yes   | De novo (high doses) | Ara C + DAUNO | - Toxicity: CC ↑acute nausea and vomiting grades 3/4 (p: 0.035, 0.010). In multivariable CC was a risk factor of vomiting (p: 0.016). Haplotype with ABCB1 G2677T/A (rs2032582) CC/GG ↑acute nausea and vomiting grades (p: 0.003; 0.026) and multivariable (0.003; 0.039) |
| He et al., 2015 [61]     | 263                          | 45.4  | 14–58       | Asian (China)    | Yes   | De novo (intermediate cytogenetic risk) | Ara C + DAUNO +/MIT | - OS, RFS: TT ↑OS (p: 0.004), ↑RFS (p: 0.019) - Haplotype with G2677T/A and C1236T: TTT ↑OS (p < 0.001), ↑RFS (p: 0.005), both maintained in multivariable analysis (p: 0.001 and 0.009). - mRNA expression: TTT haplotype ↓mRNA expression than other genotypes (p: 0.004) |
| Megías-Vericat et al., 2017 [62] | 225                        | 52.5  | 16–78       | Caucasian       | Yes   | De novo | Ara C + DAUNO     | - CR, induction death: no influence - Toxicity: TT genotype ↑renal toxicity (p: 0.008) Haplotype C3435T, G2677T/A and C1236T: TTT ↑induction death (p: 0.020), ↑renal (p: 0.016) and hepatic (p < 0.001) toxicities. |
Table 2. Cont.

| SNP          | Study                        | n     | Age (Range) | Ethnia (Country)          | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                      |
|--------------|------------------------------|-------|-------------|---------------------------|-----|----------------|---------------------|--------------------------------------------------------|
|              | Raffie et al., 2019 [63]     | 942   | 9.7 (0–30)  | Caucasian (81%) Black (13%) Asian (5%) Others (1%) | Yes | De novo        | Ara C + IDA + ETOP ± GO | - OS: in GO arm CT/TT trend to ↑ OS at 5 years (p: 0.068)  |
|              |                              |       |             |                           |     |                |                     | - EFS: in GO arm CT/TT↑EFS at 5 years (p: 0.022)         |
|              |                              |       |             |                           |     |                |                     | - DFS: in GO arm CT/TT↑DFS at 5 years (p: 0.044)          |
|              |                              |       |             |                           |     |                |                     | - RR: in GO arm CT/TT↓RR at 5 years (p: 0.007)            |
|              | * These results were observed especially at standard risk group |       |             |                           |     |                |                     |                                                        |
|              | Short et al., 2020 [64]      | 104   | 68 (24–88)  | Caucasian (86%) Black (13%) |     | NR             | GO + DAC            | - CR, ORR, CIR, OS, RFS: no influence                   |
|              | G2677T/A rs2032582 | Van den Heuvel et al., 2001 [65] | 30    | 34.6 (1–67)  | Caucasian (Netherlands) |     | Relapsed: 100  | Ara C + ANT + Others | - OS after relapse at 3 years: GT ↑OS (p: 0.02)          |
|              |                              |       |             |                           |     |                |                     | - RFS after relapse at 3 years: GT ↑RFS (p: 0.002)        |
|              |                              |       |             |                           |     |                |                     |                                                        |
|              | Illmer et al., 2002 [51]     | 405   | 53 (17–78)  | Caucasian (Germany)       | Yes | De novo        | Ara C + MIT + ETOP + AMSA | - CR: no influence.                                      |
|              |                              |       |             |                           |     |                |                     | - OS and DFS at 4 years (TX censured): no influence.      |
|              |                              |       |             |                           |     |                |                     | - Haplotype with C3435T and C1236T: wild-type ↑CR and EFS at 3 years.  |
|              |                              |       |             |                           |     |                |                     | - mRNA expression: GG ↓expression (p: 0.05)               |
|              | Kaya et al., 2005 [52]       | 28    | 36 (20–64)  | Arabs (Turkey)            |     | NR             | Ara C + ANT        | - Drug sensitive/resistant: no differences (mixed with ALL) |
|              | Kim DH et al., 2006 [53]     | 81    | 39 (15–72)  | Asian (South Korea)       | Yes | De novo        | Ara C + IDA        | - CR: GG ↑CR (p: 0.04)                                   |
|              |                              |       |             |                           |     |                |                     | - OS and EFS at 3 years (TX censured): no influence.      |
|              |                              |       |             |                           |     |                |                     | - Haplotype with C3435T: wild-type ↑CR and EFS at 3 years.  |
|              |                              |       |             |                           |     |                |                     | - mRNA expression: no influence.                          |
|              | Van der Holt et al., 2006 [54] | 150  | 67 (60–85)  | Caucasian (Netherlands)   | Yes | De novo: 79Secondary: 21 | Ara C + DAUNO | - CR, OS, EFS, DFS at 5 years: no influence.                  |
|              |                              |       |             |                           |     |                |                     | - Expression and activity of P-gp: no influence.            |
|              | Hampras et al., 2010 [56]    | 261   | 61.5 (20–85) | Caucasian (86%) Others (14%) (USA) | Yes | De novo: 75Secondary: 25 | Ara C + ANT | - OS (TX censured): no influence.                             |
|              |                              |       |             |                           |     |                |                     | - Toxicity: no influence.                                 |
|              | Kim YK et al., 2010 [66]     | 94    | 38 (17–79)  | Asian (South Korea)       |     | NR             | Ara C + IDA + BH-AC | - CR, ORR, CIR, OS, RFS: no influence                    |
|              |                              |       |             |                           |     |                |                     | - RR: GG ↑RR (p: 0.031)                                   |
|              |                              |       |             |                           |     |                |                     | - RFS: GG ↑RFS (p: 0.005)                                 |
| SNP                                      | Study                        | n   | Age (Range) | Ethnicity (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes |
|-----------------------------------------|------------------------------|-----|-------------|---------------------|-----|----------------|---------------------|-------------------|
|                                        | Green et al., 2012 [57]     | 100 | 63 (20–85)  | Caucasian (Europe)  | Yes | De novo (normal karyotype) | Ara C + ANT or MIT +/or Others | - OS at 4 years (TX censured): GG ↓ OS (p: 0.02) |
|                                        | Falk et al., 2014 [59]      | 201 | 59 (18–85)  | Caucasian (Sweden)  | Yes | De novo (normal karyotype) | Ara C + DAUNO or IDA ± ETOP +/or Others | - CR, OS, EFS: no influence FLT3 wild-type subgroup: GG ↑ OS (p: 0.039) against GT/TT genotypes. |
|                                        | He et al., 2014 [60]        | 215 | 43.6 (14–57) | Asian (China)       | Yes | De novo (normal karyotype) | Ara C (high doses) | - Toxicity: CC ↑ acute nausea and vomiting grades 3/4 (p: 0.041, 0.038). Both lost in multivariable analyses. Haplotype with ABCB1 G2677T/A (rs1045642) CC/GG ↑ acute nausea and vomiting grades 3 (0.003; 0.026) and multivariable (0.003; 0.039) |
|                                        | He et al., 2015 [61]        | 263 | 45.4 (14–58) | Asian (China)       | Yes | De novo (intermediate cytogenetic risk) | Ara C + DAUNO ± MIT | - OS, RFS: TT ↑ OS (p: 0.017), ↑ RFS (p: 0.033) - Haplotype with C3435T and C1236T: TTT ↑ OS (p < 0.001), ↑ RFS (p: 0.005), both maintained in multivariable analysis (p: 0.001 and 0.009) - mRNA expression: TTT haplotype ↓ mRNA expression than other genotypes (p: 0.004) |
|                                        | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian           | Yes | De novo (De novo) | Ara C + IDA | - CR, induction death: no influence - Toxicity: TT genotype ↑ renal (p: 0.001), hepatic (p: 0.049) toxicities & ↑ time to neutropenia recovery (p: 0.047) - Haplotype C3435T, G2677T/A and C1236T: TTT ↑ induction death (p: 0.020), ↑ renal (p: 0.016) and hepatic (p < 0.001) toxicities. |
|                                        | Rafiee et al., 2019 [63]    | 942 | 9.7 (0–30)  | Caucasian (81%)     | Yes | De novo (De novo) | Ara C + IDA + ETOP ± GO | - OS: no influence - EFS: in GO arm GT/TT/EFS at 5 years (p: 0.016) - DFS: in GO arm GT/TT ↓ DFS at 5 years (p: 0.048) - RR: in GO arm GT/TT ↓ RR at 5 years (p: 0.001) |
**Table 2. Cont.**

| SNP      | Study                                      | n   | Age (Range) | Ethnia (Country) | HWE  | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                      |
|----------|--------------------------------------------|-----|-------------|-----------------|------|----------------|---------------------|--------------------------------------------------------|
| C1236T rs1128503 | Illmer et al., 2002 [51]                    | 405 | 53 (17–78)  | Caucasian (Germany) | Yes  | De novo        | Ara C + MIT + ETOP + AMSA | CR: no influence. OS and DFS at 4 years (TX censured): no influence. Haplotype with C3435T and G2677T/A: wild-type ↓ OS and DFS at 4 years. mRNA expression: no influence. |
|          | Van der Holt et al., 2006 [51]¹           | 150 | 67 (60–85)  | Caucasian (Netherlands) | Yes  | De novo: 79Secondary: 21 | Ara C + DAUNO | CR, OS, EFS, DFS at 5 years: no influence. Expression and activity of P-gp: no influence |
|          | Hampras et al., 2010 [56]                  | 261 | 61.5 (20–85)| Caucasian (86%) Others (14%) (USA) | Yes  | De novo: 75Secondary: 25 | Ara C + ANT | OS (TX censured): no influence. Toxicity: no influence |
|          | Kim YK et al., 2010 [66]                   | 94  | 38 (17–79)  | Asian (South Korea) | NR   | De novo (t (8,21) and inv (16)) | Ara C + IDA +BH-AC | CR, RR, OS and RFS: no influence |
|          | Green et al., 2012 [57]                    | 100 | 63 (20–85)  | Caucasian (Europe) | Yes  | De novo (normal karyotype) | Ara C + ANT or MIT +/or Others | OS at 4 years(TX censured): CC ↓ OS (p: 0.03) |
|          | Scheiner et al., 2012 [58]²                | 109(44) | 34 (<1-86) | Others: White (69.7%) Non-white (30.3%) | Yes  | De novo: 72.5Secondary: 18.3 | Ara C + IDA | OS at 5 years: CC ↑ OS (p: 0.04) EFS at 5 years: CC ↑ EFS (p: 0.007) Expression and activity of P-gp: no influence |
|          | Falk et al., 2014 [59]³                    | 201 | 59 (18–85)  | Caucasian (Sweden) | Yes  | De novo (normal karyotype) | Ara C + DAUNO or IDA ± ETOP +/or Others | CR, OS, EFS: no influence. FLT3 wild-type subgroup: CC ↑ OS (p: 0.017) against CT/TT genotypes. |
|          | He et al., 2014 [60]                       | 215 | 43.6 (14–57)| Asian (China) | No   | De novo | Ara C (high doses) | Toxicity: not analyzed (excluded by HWE) |
|          | He et al., 2015 [61]                       | 263 | 45.4 (14–58)| Asian (China) | Yes  | De novo (intermediate cytogenetic risk) | Ara C + DAUNO ± MIT | OS, RFS: TT ↑ OS (p: 0.002), tRFS (p: 0.001). Haplotype with C3435T and G2677T/A: TTT ↑ OS (p < 0.001), tRFS (p: 0.005), both maintained in multivariable analysis (p: 0.001 and 0.009). mRNA expression: TTT haplotype mRNA expression greater than other genotypes (p: 0.004) |
| SNP                  | Study                  | n     | Age (Range) | Ethnicity (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes |
|---------------------|------------------------|-------|-------------|---------------------|-----|----------------|---------------------|-------------------|
| G1199A rs2229109    | Green et al., 2012 [57] | 100   | 63 (20–85)  | Caucasian (Europe)  | Yes | De novo        | Ara C + ANTI or MIT +/or Others | CR, ORR, CIR, OS, RFS: no influence |
| C174967T rs6980101  | Kim YK et al., 2007 [67]| 49    | 37 (17–69)  | Asian (South Korea) | NR  | De novo        | Ara C + IDA + ETOP +/or Others | CR: 1CT vs. CC (p: 0.03), OS, RFS, RR: no influence |
| G146792C rs10256836 | Kim YK et al., 2007 [67]| 49    | 37 (17–69)  | Asian (South Korea) | NR  | De novo        | Ara C + IDA + ETOP +/or Others | CR: 1GG vs. GC (p: 0.03), OS, RFS, RR: no influence |
| T134575A rs17327442 | Kim YK et al., 2007 [67]| 49    | 37 (17–69)  | Asian (South Korea) | NR  | De novo        | Ara C + IDA + ETOP +/or Others | CR: 1TT vs. TA (p: 0.01), OS, RFS, RR: no influence |
| A113516G rs41485732 | Kim YK et al., 2007 [67]| 49    | 37 (17–69)  | Asian (South Korea) | NR  | De novo        | Ara C + IDA + ETOP +/or Others | CR: 1AA vs. AG (p: 0.001), OS, RFS, RR: no influence |
| C193T rs121918619   | Monzo et al., 2006 [67]| 110   | 44 (16–60)  | Caucasian (Spain)   | Yes | De novo        | Ara C + IDA + ETOP +/or Others | RR: CC/CT 1RR (p: 0.02) OS at 2 years: no influence (but affect in multivariable analysis, CC 1OS) |
| lile144Met          | Monzo et al., 2006 [67]| 110   | 44 (16–60)  | Caucasian (Spain)   | NR  | De novo        | Ara C + IDA + ETOP +/or Others | RR: OS: no influence |
| SNP       | Study                  | n   | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                  |
|-----------|------------------------|-----|-------------|-----------------|-----|----------------|---------------------|-------------------------------------|
| rs3842    | Cao et al., 2017 [20]  | 206 | 67.2 (22–98)| Asian (China)   | Yes | De novo        | Ara C + ANT         | CR: no influence                     |
|           |                        |     |             |                 |     |                |                     | OS: no influence                      |
|           |                        |     |             |                 |     |                |                     | DFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | Toxicity: no influence                |
| rs2235015 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (G>T)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | DFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | RR: no influence                      |
| rs2235033 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (T>C)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | DFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | RR: no influence                      |
| rs1922242 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (A>T)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
| rs1922240 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (T>C)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | DFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | RR: no influence                      |
| rs1989830 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (C>T)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
| rs2235040 | Rafiee et al., 2019 [63]| 942 | 9.7 (0–30)  | Caucasian       | Yes | De novo        | Ara C + IDA + ETOP ± GO | OS: no influence                     |
| (G>A)     |                        |     |             | (81%) Black (13%) Asian (5%) Others (1%) |     |                |                     | EFS: no influence                     |
| ABCB11    |                        |     |             |                 |     |                |                     | DFS: no influence                     |
|           |                        |     |             |                 |     |                |                     | RR: no influence                      |
| rs4668115 | Drenberg et al., 2016 [13] | 164 | 9.1 (0–21)  | White (70%) Black (20%) Others (10%) |     | De novo        | Ara C + DAUNO + ETOP + MIT | OS: GG ↓ OS (p: 0.03) |
| (G>A)     |                        |     |             |                 |     |                |                     | EFS: GG ↓ EFS (p: 0.05)                  |
| ABC1      |                        |     |             |                 |     |                |                     |                                      |
| T2684C    | Mahjoubi et al., 2008 [82] | 111 | NR          | Arabs (Iran)    |     | 52 AMLNR       | NR                   | CR: no influence                     |
|           |                        |     |             |                 |     |                |                     | Expression of ABC1 related to lower CR, drug sensitive and R/R rate |
| C2007T    | Mahjoubi et al., 2008 [82] | 111 | NR          | Arabs (Iran)    |     | 52 AMLNR       | NR                   | CR: no influence                     |
| rs2301666 |                        |     |             |                 |     |                |                     | Expression of ABC1 related to lower CR, drug sensitive and R/R rate |
| G2012T    | Mahjoubi et al., 2008 [82] | 111 | NR          | Arabs (Iran)    |     | 52 AMLNR       | NR                   | CR: no influence                     |
| rs45511401|                        |     |             |                 |     |                |                     | Expression of ABC1 related to lower CR, drug sensitive and R/R rate |
Table 2. Cont.

| SNP       | Study                          | n    | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                                                 |
|-----------|-------------------------------|------|------------|-----------------|-----|----------------|---------------------|----------------------------------------------------------------------------------|
| C2665T    | Mahjoubi et al., 2008 [82]    | 111  | NR         | Arabs (Iran)    | NR  | 52 AMLNR       | NR                  | - CR: no influence                                                             |
|           |                               |      |            |                 |     |                |                     | - Expression of ABCC1 related to lower CR, drug sensitive and R/R rate          |
| T825C     | Hampras et al., 2010 [56]     | 261  | 61.5 (20–85) | Caucasian (86%) (USA) | Yes | De novo: 75Secondary: 25 | Ara C + ANT | - OS (TX censored): no influence |
| rs246221  |                               |      |            | Others (14%) (USA) |     |                |                     | - Toxicity: no influence                                                        |
| T1062C    | Hampras et al., 2010 [56]     | 261  | 61.5 (20–85) | Caucasian (86%) (USA) | Yes | De novo: 75Secondary: 25 | Ara C + ANT | - OS (TX censored): no influence |
| rs35587   |                               |      |            | Others (14%) (USA) |     |                |                     | - Toxicity: no influence                                                        |
| G4002A    | Hampras et al., 2010 [56]     | 261  | 61.5 (20–85) | Caucasian (86%) (USA) | Yes | De novo: 75Secondary: 25 | Ara C + ANT | - OS (TX censored): no influence |
| rs2230671 |                               |      |            | Others (14%) (USA) |     |                |                     | - Toxicity: no influence                                                        |
| rs4148350 | Megías-Vericat et al., 2017 [62] | 225  | 52.5 (16–78) | Caucasian         | Yes | De novo         | Ara C + IDA         | - CR, induction death: no influence |
|           |                               |      |            |                 |     |                |                     | - Toxicity: wild-type GG ↑hepatic severe toxicity grade 3–4 (p: 0.044)           |
| rs129081  | Kunadt et al., 2020 [83]      | 160  | 46 (18–60)  | Caucasian (Germany) | Yes | NK AMLDe novo: 93.1Secondary: 6.9 | Ara C + DAUNO | - CR: no influence |
| (C>G)     |                               |      |            |                 |     |                |                     | - OS: GG/O 98:7 at 5 years (p: 0.035)                                          |
| rs212090  | Cao et al., 2017 [20]         | 206  | 67.2 (22–98) | Asian (China)    | Yes | De novo         | Ara C + ANT         | - DFS: TT ↑DFS at 5 years (p: 0.021)                                           |
| (A>T)     |                               |      |            |                 |     |                |                     | - RR: no influence                                                             |
| rs212091  | Cao et al., 2017 [20]         | 206  | 67.2 (22–98) | Asian (China)    | Yes | De novo         | Ara C + ANT         | - Toxicity: AT ↑gastrointestinal toxicity (p: 0.010)                           |
| (A>G)     |                               |      |            |                 |     |                |                     |                                                                                |
| rs129091  | Kunadt et al., 2020 [83]      | 160  | 46 (18–60)  | Caucasian (Germany) | Yes | NK AMLDe novo: 93.1Secondary: 6.9 | Ara C + DAUNO | - CR: no influence |
|           |                               |      |            |                 |     |                |                     | - OS: no influence                                                            |
| rs212089  | Cao et al., 2017 [20]         | 206  | 67.2 (22–98) | Asian (China)    | Yes | De novo         | Ara C + ANT         | - DFS: TT ↑DFS at 5 years (p: 0.021)                                           |
|           |                               |      |            |                 |     |                |                     | - RR: no influence                                                             |
|           |                               |      |            |                 |     |                |                     | - Toxicity: no influence                                                        |
| rs212091  | Kunadt et al., 2020 [83]      | 160  | 46 (18–60)  | Caucasian (Germany) | Yes | NK AMLDe novo: 93.1Secondary: 6.9 | Ara C + DAUNO | - CR: no influence |
| (A>G)     |                               |      |            |                 |     |                |                     | - OS: GG ↓OS at 5 years (p: 0.006)                                            |
|           |                               |      |            |                 |     |                |                     | - DFS: GG ↓DFS at 5 years (p: 0.016)                                           |
|           |                               |      |            |                 |     |                |                     | - RR: no influence                                                             |
|           |                               |      |            |                 |     |                |                     | - Toxicity: no influence                                                        |
| SNP       | Study                  | n   | Age (Range) | Ethnicity (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                                                 |
|-----------|------------------------|-----|-------------|---------------------|-----|----------------|---------------------|-----------------------------------------------------------------------------------|
| rs3743527 (C>T) | Cao et al., 2017 [20]  | 206 | 67.2 (22–98) | Asian (China)        | Yes | De novo        | Ara C + ANT           | - CR: no influence - OS: no influence - RFS: no influence - Toxicity: TT ↑myelosuppression (p: 0.007) |
| rs4148380 (G>A) | Cao et al., 2017 [20]  | 206 | 67.2 (22–98) | Asian (China)        | Yes | De novo        | Ara C + ANT           | - CR: no influence - OS: no influence - RFS: no influence - Toxicity: no influence |
| ABCC2     |                        |     |             |                     |     |                |                     |                                                                                  |
| G4544A    | Megías-Verical et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian           | Yes | De novo        | Ara C + IDA           | - CR, induction death: no influence - Toxicity: no influence                     |
| rs1989983 (G>A) | Yee et al., 2013 [16]  | 54  | NR          | Caucasian (Europe)  | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX) | - DFS (preTX): GG ↓DFS (p: 9.45 × 10^{-6}; remained significant after Bonferroni correction). No influence in non-Caucasian cohort |
| rs2301835 (C>T) | Yee et al., 2013 [16]  | 154 | NR          | Caucasian (Europe)  | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX) | - DFS (preTX): TT ↑DFS (p: 0.0029). No influence in non-Caucasian cohort |
| rs2277624 (A>G) | Yee et al., 2013 [16]  | 154 | NR          | Caucasian (Europe)  | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX) | - DFS (preTX): AA ↓DFS (p: 0.004). No influence in non-Caucasian cohort |
| rs8079740 (A>G) | Yee et al., 2013 [16]  | 154 | NR          | Caucasian (Europe)  | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX) | - DFS (preTX): GG ↓DFS (p: 0.0078). No influence in non-Caucasian cohort |
| rs757420 (T>C) | Yee et al., 2013 [16]  | 154 | NR          | Caucasian (Europe)  | NR  | NR             | Ara C + ETOP + BUSUL (pre-TX) | - DFS (preTX): TT ↑DFS (p: 0.0079). No influence in non-Caucasian cohort |
| C211T    | Müller et al., 2008 [18] | 139 | 46.3 (15–86) | Jews (61.2%) Arabs (38.8%) | Yes | De novo        | Ara C + ANT ± FLUDA ± MIT | - OS (TX censured): CC ↓OS (p: 0.018) |
| rs4793665 | Butrym et al., 2021 [88] | 95  | 61 (22–90)  | Caucasian (Poland)  | Yes | De novo        | Ara C + DAUNO or low dose Ara C or AZA | - CR: no influence - OS: no influence |

Table 2. Cont.
Table 2. Cont.

| SNP             | Study                                | n     | Age          | Ethnia (Country) | HWE  | LMA Status (%) | Chemotherapy Scheme                     | Clinical Outcomes                                                                 |
|-----------------|--------------------------------------|-------|--------------|-----------------|------|----------------|----------------------------------------|------------------------------------------------------------------------------------|
| ABCG2           | Hampras et al., 2010 [56]            | 261   | 61.5 (20–85) | Caucasian (86%) | NR   | De novo: 75%   | Secondary: 25% Ara C + ANT             | OS (TX censored); GG ↓ OS (p: 0.05) Toxicity: AA/AG ↑ risk of toxicity grade 3 or more |
|                 | Wang et al., 2011 [97]               | 141   | 32 (5–70)    | Asian (China)   | NR   | De novo: Mixed with ALL Ara C + DAUNO/MITO | -                                                                                   |
|                 | Megías-Vericat et al., 2017 [62]     | 225   | 52.5 (16–78) | Caucasian       | Yes  | De novo: Ara C + IDA | -                                                                                   |
|                 | Muller et al., 2008 [18]             | 139   | 46.3 (15–86) | Jews (61.2%)    | Yes  | De novo: Ara C + ANT + FLUDA ± MIT | -                                                                                   |
|                 | Hampras et al., 2010 [56]            | 261   | 61.5 (20–85) | Caucasian (86%) | Yes  | De novo: 75%   | Secondary: 25% Ara C + ANT             | CR: trend to GG ↑ CR (p: 0.053), Mixed with ALL patients OS: GG/OS (p < 0.001), Mixed with ALL patients DFS: GC/DFS (p < 0.001), Mixed with ALL patients Haplotype GG (rs2231137) with CA (rs2231142) and CT (rs2231149) ↓ DFS/OS (p < 0.001) |
|                 | Wang et al., 2011 [97]               | 141   | 32 (5–70)    | Asian (China)   | NR   | De novo: Mixed with ALL Ara C + DAUNO/MITO | -                                                                                   |
|                 | Tiribelli et al., 2013 [98]          | 125   | 59.2 (20–84) | Caucasian (Italy)| Yes  | NR Ara C + IDA + FLUDA ± ETOP | -                                                                                   |
|                 | Megías-Vericat et al., 2017 [62]     | 225   | 52.5 (16–78) | Caucasian       | Yes  | De novo: Ara C + IDA | -                                                                                   |
|                 | Wang et al., 2011 [97]               | 141   | 32 (5–70)    | Asian (China)   | NR   | De novo: Mixed with ALL Ara C + DAUNO/MITO | -                                                                                   |
|                 | Ile619Ile (C>T) Wang et al., 2011 [97]| 141   | 32 (5–70)    | Asian (China)   | NR   | De novo: Mixed with ALL Ara C + DAUNO/MITO | -                                                                                   |
Table 2. Cont.

| SNP          | Study                   | n    | Age (Range) | Ethnia (Country) | HWE  | LMA Status (%) | Chemotherapy Scheme                          | Clinical Outcomes                                         |
|--------------|-------------------------|------|-------------|-----------------|------|----------------|-----------------------------------------------|----------------------------------------------------------|
| rs2231149 (C>T) | Wang et al., 2011 [97] | 141  | 32 (5–70)   | Asian (China)    | NR   | De novo Mixed with ALL | Ara C + DAUNO/MITO           | - CR: no influence. Mixed with ALL patients                |
|              |                         |      |             |                 |      |                |                                               | - OS: CC?OS (p < 0.01; lost in multivariate analysis)     |
|              |                         |      |             |                 |      |                |                                               | Mixed with ALL patients                                    |
|              |                         |      |             |                 |      |                |                                               | Mixed with ALL patients                                    |
|              |                         |      |             |                 |      |                |                                               | - DFS: CC↑ (p < 0.05; lost in multivariate analysis)       |
|              |                         |      |             |                 |      |                |                                               | Mixed with ALL patients                                    |
|              |                         |      |             |                 |      |                |                                               | Mixed with ALL patients                                    |
|              |                         |      |             |                 |      |                |                                               | Haplotype GG (rs2231137) with CA (rs2231142) and CT (rs2231149) ↓DFS/OS (p < 0.001) |
| rs2231162 (C>T) | Wang et al., 2011 [97] | 141  | 32 (5–70)   | Asian (China)    | NR   | De novo Mixed with ALL | Ara C + DAUNO/MITO           | - CR, OS, DFS: no influence. Mixed with ALL patients   |
|              |                         |      |             |                 |      |                |                                               |                                                          |
| rs2231164 (C>T) | Wang et al., 2011 [97] | 141  | 32 (5–70)   | Asian (China)    | NR   | De novo Mixed with ALL | Ara C + DAUNO/MITO           | - CR, OS, DFS: no influence. Mixed with ALL patients   |
|              |                         |      |             |                 |      |                |                                               |                                                          |

Abbreviations: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; AMSA: amsacrine; ANT: anthracycline; AZA: azacitidine; BH-AC: N4-behenoyl-1D-arabinofuranosycytosine; BUSUL: busulfan; CIR: cumulative incidence of relapse; CR: complete remission; DAC: decitabine; DAUNO: daunorubicin; DFS: disease-free survival; EFS: event-free survival; ETOP: etoposide; FLUDA: fludarabine; GO: gemtuzumab ozogamicin; HWE: Hardy–Weinberg equilibrium; IDA: idarubicin; MIT: mitoxantrone; NK: normal karyotype; NR: not reported; ORR: overall response rate; OS: overall survival; RFS: relapse-free survival; RR: rate of relapse; R/R: relapse/refractory; TX: hematologic transplant. 1—Allele frequency and treatment outcomes only reported in 115 patients for C1236T, 142 patients for G2677T/A and 130 patients for C3435T. 2—Allele frequency only reported in 103 patients and treatment outcomes only in 44 patients (AML M3 subtype, secondary AML and patients with comorbidities or poor performance status were excluded). 3—A total of 100 patients were previously collected and published in Green et al., 2012 [57]. 4—This study [13] analyzed 1936 SNPs of 225 genes with a multi-SNP-based approach (including ABC and SLC transporters). Only SNPs with significant results were cited. 5—This study [83] included 48 SNPs within 7 genes of 7 ABC transporters (ABCA2, ABCA3, ABCB1, ABCB2, ABCB5, ABCB7 and ABCC1), but only specified the SNPs with significant effect. 6—This study [16] analyzed 1659 SNPs of 42 genes with a multi-SNP-based approach. Only SNPs with significant results were cited.

3.3. SNP-SNP Combinations of Transporters

Most of the included pharmacogenetic studies employed the candidate genes approach based on the pharmacologic pathway of the drugs. The drug intake depends on the combination of input and output transporters, but only a few studies analyzed the genetic variability of both types of carriers together. A recent study explored the combination of SLC wild-type genotypes (functional SLCO1B1 and/or SLC22A16), ensuring the anthracycline uptake in cells, with the variant genotypes of ABC pumps (defective expression of ABCB1, ABCC1, ABCC2 or ABCG2), avoiding anthracycline expulsion [14]. Several novel findings were reported with the combinations of ABCB1 and SLC polymorphisms, including higher hepatic and renal toxicities, mucositis and neutropenia, as well as a higher incidence of induction death (Table 3). All of these are probably associated with a higher intracellular idarubicin accumulation and have been previously reported with ABCB1 SNPs [62]. In addition, the combination of the SLC22A16 rs714368 wild-type genotype with the variant allele of ABCG2 rs2231142 was related to a higher cardiac toxicity (Table 3), reproducing the previous association [62]. On the other hand, no associations were found with ABCC1 rs4148350 and ABC2 rs8187710 SNPs combined with SLCO1B1/SLC22A16 wild-type genotypes. Combinations of SLCO1B1 and ABC polymorphisms were also described with irinotecan [99,100] and statins [101,102]. Regarding cytarabine intake, two different studies analyzed the combined influence of SNPs in SLC29A1 with genes of the main enzymes of the cytarabine pathway (DCK, CDA, etc.) [43,44], but the combination with ABC pumps was not explored.
Table 3. Characteristics of the studies included in the systematic review for SNP–SNP combinations of ABC and SLC transporters.

| SNP                        | Study                                         | n   | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes                                                                 |
|---------------------------|-----------------------------------------------|-----|-------------|------------------|-----|----------------|---------------------|----------------------------------------------------------------------------------|
| **ABCB1 + SLC**           |                                               |     |             |                  |     |                |                     |                                                                                  |
| **ABCB1 C3435T rs1045642**| Megías-Vericat et al., 2017 [62]              | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR, induction death: no influence |
| **SLC01B1 rs4149056 (T>C)**|                                               |     |             |                  |     |                |                     | Toxicity: TT + TT genotype ↑hepatic toxicity (p: 0.038) |
| **ABCB1 C3435T rs1045642**|                                               | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR, induction death: no influence |
| **SLC22A16 rs12210538 (A>G)**|                                               |     |             |                  |     |                |                     | Toxicity: TT + AA genotype ↑hepatic toxicity (p: 0.019), mucositis (p: 0.004), neutropenia (p: 0.034) |
| **ABCB1 G2677T/A rs2032582**|                                               | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR, induction death: no influence |
| **SLC01B1 rs4149056 (T>C)**|                                               |     |             |                  |     |                |                     | Toxicity: TT + TT genotype ↑renal (p: 0.030), hepatic toxicity (p: 0.002) |
| **ABCB1 G2677T/A rs2032582**|                                               | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR, induction death: no influence |
| **SLC22A16 rs12210538 (A>G)**|                                               |     |             |                  |     |                |                     | Toxicity: TT + AA genotype ↑renal (p: 0.026), hepatic toxicity (p: 0.008) |
| **ABCB1 G2677T/A rs2032582**|                                               | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR, induction death: no influence |
| **SLC22A16 rs714368 (A>G)**|                                               |     |             |                  |     |                |                     | Toxicity: TT + AA genotype ↑renal (p: 0.026), hepatic toxicity (p: 0.008) |
| **ABCB1 C1236T rs1128503**|                                               | 225 | 52.5 (16–78) | Caucasian        | Yes | De novo        | Ara C + IDA         | CR: no influence |
| **SLC01B1 rs4149056 (T>C)**|                                               |     |             |                  |     |                |                     | Induction death: TT + TT genotype ↑induction death (p: 0.018) |
|                           |                                               |     |             |                  |     |                |                     | Toxicity: TT + TT genotype ↑renal (p: 0.048), hepatic toxicity (p < 0.001) |
| SNP | Study | n  | Age (Range) | Ethnia (Country) | HWE | LMA Status (%) | Chemotherapy Scheme | Clinical Outcomes |
|-----|-------|----|-------------|------------------|-----|----------------|---------------------|-------------------|
| **ABCB1 haplotype**<sup>1</sup>  
**SLCO1B1 rs4149056 (T>C)** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR: no influence  
- Induction death: TT/TT/TT + TT genotype ↑induction death (p: 0.009)  
- Toxicity: TT/TT/TT + TT genotype ↑renal (p: 0.017), hepatic toxicity (p < 0.001) |
| **ABCB1 haplotype**<sup>1</sup>  
**SLC22A16 rs12210538 (A>G)** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR, induction death: no influence  
- Toxicity: TT/TT/TT +AA genotype ↑renal (0.036), hepatic toxicity (p: 0.015) |
| **ABCB1 haplotype**<sup>1</sup>  
**SLC22A16 rs714368 (A>G)** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR, induction death: no influence  
- Toxicity: TT/TT/TT +AA genotype ↑hepatic toxicity (p: 0.001) |
| **ABCC1 + SLC** | | | | | | | | |
| **ABCC1 rs4148350  
SLCO1B1/SLC22A16** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR, induction death: no influence  
- Toxicity: no influence |
| **ABCC2 + SLC** | | | | | | | | |
| **ABCC2 rs8187710  
SLCO1B1/SLC22A16** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR, induction death: no influence  
- Toxicity: no influence |
| **ABCG2 + SLC** | | | | | | | | |
| **ABCG2 rs2231142 (C>A)  
SLC22A16 rs714368 (A>G)** | Megías-Vericat et al., 2017 [62] | 225 | 52.5 (16–78) | Caucasian | Yes | De novo | Ara C + IDA | - CR, induction death: no influence  
- Toxicity: AC + AA genotype ↑cardiac toxicity (p: 0.033) |

Abbreviations: AML: acute myeloid leukemia; CR: complete remission; HWE: Hardy–Weinberg equilibrium; IDA: idarubicin; NR: not reported; OS: overall survival. <sup>1</sup>The **ABCB1** haplotype included the polymorphisms rs1128503, rs1045642 and rs2032582.
4. Conclusions

Transporters of the SLC and ABC families play crucial roles in the absorption, disposition and elimination of antineoplastic drugs. In AML, the expression of these transporters has been proposed as one of the main drug resistance mechanisms and has been widely studied for standard chemotherapy 3 + 7 schedules based on anthracyclines and cytarabine. However, the impact of genetic variability in the SLC and ABC genes remains controversial. This review aims is to demonstrate that polymorphisms in transporter genes may have a potential impact on the clinical outcomes of AML therapy.

Despite this, only a few studies have analyzed the role of SLC carriers in AML therapy; promising findings were obtained with polymorphisms in the SLCO1B1 and SLC29A1 genes. Variant alleles of SLCO1B1 were correlated with a lower function, decreasing anthracycline hepatic uptake and metabolism [10,11] and showed higher survival rates and toxicity in AML studies [5,13,14]. Polymorphisms of SLC29A1, responsible for cytarabine uptake, showed a relevant impact on CR and survival rates, especially in Asian populations [20,42–45].

Meanwhile, the variant alleles of ABCB1 have been widely studied in AML, demonstrating a clear association with lower pump function, as well as higher CR and survival rates in meta-analyses [73,74]. The influence of ABCB1 polymorphisms in anthracycline-related toxicities remains more controversial in AML, with scarce relevant findings [60,62] and without evidence of higher cardiotoxicity unlike studies in other malignancies [22,23,75,76]. Encouraging relationships were discovered in AML studies with ABCCI [20,62,82,83] and ABCG2 polymorphisms [56,62,97,98].

SNP–SNP combinations of transporters could play a crucial role in characterizing the anthracycline pathway, which involves complex pharmacokinetic and pharmacodynamic mechanisms, although this was only evaluated in a Caucasian AML cohort [14]. In addition, it has been hypothesized that SNP–SNP combinations could increase the power of detection of significant associations where individual SNPs of SLC or ABC genes only demonstrate a minor effect that could be affected by their combination [103]. Combinations of transporters with other relevant SNPs such as enzymes have been explored in previous studies in AML with cytarabine [43,44].

The influence of ABC pumps in anthracycline pharmacokinetics has been suggested in vitro [70,80] and studies in other cancers [47], but a population pharmacokinetic study performed in AML failed to reproduce these findings with ABCB1 and ABCG2 polymorphisms [68]. Furthermore, the AML studies included did not analyze the influence of transporter SNPs together in drug pharmacokinetic levels and clinical response. In this line, a study in AML demonstrated a correlation between cytarabine plasma level and CDA genotype, the main enzyme responsible for liver metabolism of cytarabine [104]. In chronic myeloid leukemia, a relevant decrease in imatinib clearance was associated with variant alleles of ABCB1 and SLCO1B3 [105]. Similarly, in acute lymphoblastic leukemia, the SLCO1B1 521T>C SNP reduced methotrexate clearance [106]. Previous reviews focused on the impact of ABC and SLC SNPs in drug bioavailability have found the same limited evidence of PK studies in the AML context [47,107,108].

The influence of genetic variability in AML therapy has been previously analyzed by other authors, especially focused of the main SNPs of the cytarabine and anthracycline metabolic pathways [3,4,109,110] or only in SNPs of transporter genes [47,107,108,111]. Pinto et al. [112] recently performed a systematic review of the general state of pharmacogenetics in AML including, as a novelty, polymorphisms with a potential impact in new targeted therapies (e.g., FLT3 inhibitors, GO, hypomethylating agents and IDH inhibitors). On the other hand, our review centers on evaluating the influence of polymorphisms in transporter genes (SLC and ABC and their combinations) in AML studies, which was briefly explained in this recent review [112].

Most of the reported pharmacogenetic studies were performed in patients treated with a standard 3 + 7 scheme with a candidate genes approach. The importance of pharmacogenetics for the multiple new drugs recently approved for AML treatment remains
unknown. Although these therapies are more tolerable than classical antineoplastics, potential drug–drug interactions involving P-gp, BCRP and OATP transporters have been described [113]. The genetic variability of SLC and ABC genes should be analyzed in further studies involving these novel therapies. In this line, a higher response to gemtuzumab ozogamicin was reported with the variant alleles of ABCB1 in a pediatric cohort [63], but no influence was observed in adult AML patients treated with gemtuzumab ozogamicin and decitabine [64].

In conclusion, pharmacogenetic studies based on candidate genes have reported relevant associations between SNPs in transporters (SLC and ABC) with AML outcomes and safety profiles. Unfortunately, most of these studies were observational and involved retrospective cohorts, and only anecdotally were these transporter genes analyzed together with metabolic enzymes, molecular targets and DNA repair genes. In the future, randomized clinical trials on larger populations including those of different age, ethnic and therapy groups should be developed in order to validate the clinical benefit of pharmacogenetics in AML patients.

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