Multidrug-related protein 1 (MRP1) polymorphisms rs129081, rs212090, and rs212091 predict survival in normal karyotype acute myeloid leukemia

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Abstract
Resistant disease is still a main obstacle in acute myeloid leukemia (AML) treatment. Therefore, individual genetic variations affecting therapy response are gaining increasing importance. Both SNPs and ABC transporter genes could already be associated with drug resistance. Here, we report allelic variants of MRP1 (ABCC1) SNPs rs129081, rs212090, and rs212091 with significant influences on survival in AML patients. DNA was extracted from bone marrow samples (n = 160) at diagnosis. Genotyping 48 SNPs within seven different ABC transporter genes using real-time PCR revealed rs129081 GG variant with a significant higher OS (p = 0.035) and DFS (p = 0.01). Comparing TT and AA rs212090 variants showed significant influences on DFS (p = 0.021). SNP rs212091 GG expression was associated with worse OS (p = 0.006) and a significant difference in DFS between alleles GG and AA (p = 0.018). The multivariable models confirmed a significant influence on OS for rs212091 (AA HR = 0.296, 95% CI 0.113–0.774, p = 0.013 and GG p = 0.044). Rs129081 variant CG, TT of rs212090, AA, and AG of rs212091 demonstrated significant impact on DFS (p = 0.024, p = 0.029, p = 0.017, and p = 0.042, respectively). This analysis demonstrates a significant influence of MRP1 SNPs on survival in AML. As they were not associated to prognostic characteristics, we suggest these SNPs to be independent prognostic markers for AML.

Keywords Acute myeloid leukemia · Multidrug resistance · MRP1 · SNPs · Prognosis · Survival

Background
Acute myeloid leukemia (AML) is characterized by uncontrolled proliferation of undifferentiated myeloid blasts requiring rapid induction chemotherapy to induce a remission. Although approximately 75% of patients achieve complete remission (CR) after induction treatment consisting of cytarabine (100 mg/m², days 1–7) and daunorubicin (60 mg/m², on three consecutive days), two-thirds of AML patients under the age of 60 relapse after successful induction chemotherapy, with an even higher rate in older patients [1–3]. Drug resistance affecting standard chemotherapeutic compounds in AML results in induction failure or relapse. Very often relapse presents with a highly aggressive AML clone insensitive to salvage chemotherapy with the urgent need of intensified treatment and more invasive procedures like allogeneic stem cell transplantation, thus far the only available curative option for these patients.

Molecular mechanisms causing therapy failure leading to inferior prognosis of AML patients are still incompletely
understood and one of the most difficult obstacles in AML therapy. Within the context of clinically relevant inter-individual differences in treatment response or susceptibility to cytostatic agents and other drugs alike, single nucleotide polymorphisms (SNPs) were identified as individual genetic variations accountable for treatment failure. Several of these polymorphisms have already been described with different therapy outcomes, individual alterations of pharmaceutical responses like an elevated risk of chemoresistance, and risk to develop a malignancy in general and AML alike [4–8]. For example, SNPs located within cytarabine metabolizing enzyme genes were associated with therapeutic effects concerning AML patients’ outcome [9]. Illmer et al. could further demonstrate a significant impact of ABCB1 (MDR1, P-glycoprotein) SNPs on therapy outcome in AML patients [4].

Transmembrane ATP-binding cassette transporters (ABC transporters) are important for substrate efflux and therefore providing a physiological function in multiple tissues, protecting cells against toxic metabolites. Some ABC transporters have certain substrate specificities for anticancer drugs, especially for cytarabine and daunorubicin. For cytarabine experimental analyses revealed that certain ABC transporter expressions lead to lower drug levels in leukemic blasts and thereby causing poor therapy response or even drug resistance [10].

ABC transporters have been extensively associated with the underlying principle of a so-called multidrug resistance (MDR), causing resistance to both multiple physiologic substrates and therapeutic drugs alike, leading to therapy failure, disease progression, and resistant disease [11–13].

ABC transporters ABCB1, ABCC1 (MRP1), and ABCG2 (BCRP) could be identified as the main MDR-generating transporters within the ABC family characterized by a very broad range of substrates and substrate specificity [11, 12, 14]. Furthermore, ABCC11 (MRP8) mRNA expression in blast progenitor cells of AML patients was demonstrated to have a significant influence on treatment response and long-term survival by conferring resistance to cytarabine [15].

Hence, the goal of this study was to further investigate whether so far non-investigated SNPs located within ABC-transporter genes responsible for daunorubicin efflux have an impact on treatment outcome in intensively treated younger AML patients.

### Patients and methods

This analysis included AML patients (non-APL AML) within the prospective AML2003 trial (NCT00180102) for patients under the age of 60 years with a normal karyotype (NK) from whom bone marrow aspirate with sufficient DNA extraction was available. Bone marrow aspirates obtained at diagnosis from a total of 160 Caucasian AML patients according to WHO criteria were investigated [16]. Written informed consent was obtained from all patients and the study was approved by the local ethics committee of the University of Dresden (EK153092003). The patients’ characteristics are summarized in Table 1. The median age at diagnosis was...
Results

A significant impact on major outcomes (OS and DFS) was detected for three ABC transporter SNPs rs129081 (CACCC[C/G]ACTCCA), rs212090 (TTACTG[A/T]TCCCAC), and rs212091 (ACCTTA[A/G]AGAACA).

Patients carrying the homozygous rs129081 GG-SNP (n = 65) had a significant higher 5-year-OS and 5-year-DFS, compared to the homozygous wild type CC (n = 27) and heterozygous CG (n = 68) patients (OS: GG 68% [95% CI 55–80%] vs. CC 40% [95% CI 18–61%] vs. CG 64% [95% CI 52–75%], p = 0.035; DFS: GG 64% [95% CI 50–77%] vs. CC 35% [95% CI 16–53%] vs. CG 50% [95% CI 38–62%], p = 0.01) in univariate analysis, Figs. 1 and 2. Although these results did not have a significant impact on OS in multivariable analysis (Table 2), heterozygous CG demonstrated a significant impact on DFS in multivariable analysis (p = 0.024), while the other allele variants of rs129081 had no independent influence on DFS (Table 3).

For allele variants of SNP rs212090 (AA n = 38, AT n = 80, TT n = 42), no statistically significant impact on OS both in univariate and multivariate testing was observed (AA 66% [95% CI 50–82%] vs. AT 64% [95% CI 53–75%] vs. TT 50% [95% CI 33–68%], p = 0.289, Fig. 3 and Table 2), but a trend towards worse OS for genotype TT could be identified. Although rs212090 showed no significant influence on DFS with genotype TT leading to shortest DFS (AA 68% [95% CI 52–83%] vs. AT 52% [95% CI 41–64%] vs. TT 40% [95% CI 25–55%], p = 0.064, Fig. 4), it revealed a significant

![Figure 1](image-url)
difference in DFS when comparing homozygous alleles AA and TT ($p = 0.021$) in univariate testing. The significant impact of homozygous variant TT of rs212090 on DFS was confirmed in multivariate analysis ($p = 0.029$, HR $2.321$, 95% CI $1.092$–$4.932$, Table 3), respectively.

SNP rs212091 showed a significant difference for OS with the homozygous allele GG ($n = 6$) leading to inferior OS (GG 0% vs. AA 64% [95% CI 55–74%] vs. AG 59% [95% CI 44–75%], $p = 0.006$, Fig. 5). In multivariable testing, an independent influence on OS for AA ($n = 114$, $p = 0.044$) and GG (HR $= 0.296$, 95% CI $0.113$–$0.774$, $p = 0.013$) was demonstrated (Table 2). Regarding DFS for rs212091, no significant influence could be demonstrated in a univariate model (AA 55% [95% CI 46–65%] vs. 49% AG [95% CI 33–64%] vs. GG 0%, $p = 0.058$, Fig. 6). Comparing the homozygous genotypes of rs212091, GG was correlated with a significant reduction of DFS in contrast to homozygous counterpart AA (GG 0% vs. AA 55%, $p = 0.018$). These findings could be confirmed in
multivariable analysis with independent significant impact on DFS for GG (HR = 0.28, 95% CI 0.098–0.797, \( p = 0.017 \)) and AG (HR = 0.312, 95% CI 0.101–0.958, \( p = 0.042 \)), Table 3.

A total of 78% (\( n = 125 \)) of the here analyzed study cohort achieved CR. CR rate was not affected by these \( \text{MRP1} \) polymorphisms (\( \text{rs129081} \) \( p = 0.078 \), \( \text{rs212090} \) \( p = 0.148 \), \( \text{rs212091} \) \( p = 0.420 \)). A trend towards a higher incidence of relapse of the investigated SNP variants was in accordance with worse OS and DFS, respectively, but did not reach statistical significance (\( p = 0.152 \), \( p = 0.426 \), and \( p = 0.231 \)).

Furthermore, our data also showed that there were no significant differences of standard clinical baseline characteristics, \( \text{FLT3-ITD} \), or \( \text{NPM1} \) mutation status in the above described SNP groups. Regarding the combination of a co-occurring \( \text{FLT3-ITD} \) and \( \text{NPM1} \) mutation, \( \text{rs129081} \), \( \text{rs212090} \), and \( \text{rs212091} \) allele variants were not significantly associated with a \( \text{FLT3-ITD/NPM1} \) co-expression (Table 4). Though SNP \( \text{rs212090} \) alleles were characterized with significant differences in \( \text{FLT3-ITD} \) ratio, differences in \( \text{FLT3-ITD} \) ratios of \( \text{rs129081} \) and \( \text{rs212091} \) did not reach statistical significance (Table 4).

The patients’ age had no influence on the investigated \( \text{MRP1} \) polymorphisms (\( \text{rs129081} \): \( p = 0.962 \), \( \text{rs212090} \): \( p = 0.585 \), \( \text{rs212091} \): \( p = 0.706 \)). The quality and intensity of toxicities according to CTCAE after chemotherapy were not significantly different between allele variants. Genotype frequencies of \( \text{rs129081} \), \( \text{rs212090} \), and \( \text{rs212091} \) were in accordance with the Hardy-Weinberg equation. Calculation of the linkage disequilibrium identified linked SNPs (\( \text{rs129081/rs212090} \) \( p = 0 \), \( D^{'1} = 1 \); \( \text{rs129081/rs212091} \) \( p = 0 \), \( D^{'1} = 1 \); and \( \text{rs212090/rs212091} \) \( p = 1.62^{14} \), \( D^{'1} = 1 \), respectively).

**Discussion**

As AML presents clinically as a very heterogeneous hematopoietic malignancy with considerable variations in treatment
response and patient outcome, prognostic markers need to be identified to offer individualized and risk-stratified therapy options to improve survival. Therapy resistance with progressive disease and limited therapeutic options still remains a major obstacle in the treatment of AML patients. Especially younger AML patients which represent a population with curative potential and long-term remission after intensive treatment, still need further adjusted treatment, as a considerable number of younger patients also suffer from progressive disease and relapse, but are uniformly treated with daunorubicin and cytarabine [20]. The clinical dilemma and pressure is about identifying mechanisms of these chemotherapy-resistances. During the last decade, several molecular prognostic factors for AML have been detected and included in standard routine diagnostics leading to improved risk stratification and prognosis evaluation and therefore adjusted therapeutic approaches [21–23]. With this analysis, we identified promising predictors for OS and DFS with SNP rs129081, rs212090, and rs212091 in NK-AML patients and indicate these SNPs to be prognostic markers for OS and DFS, respectively.

MRP1 SNPs rs129081, rs212090, and rs212091 are located within the 3′UTR region of the MRP1 transporter gene and therefore cause no primary change in amino acid sequence. As the 3′UTR region is a binding site for regulatory miRNAs, the influence of these SNPs by altering DNA sequence could unfold on a post-transcriptional level with different miRNAs leading to modification of the synthesized DNA strand and hereby potentially altering protein structures of ABC transporters after DNA transcription. In solid tumors as well as in AML, miRNAs have been identified as critical multiple key elements in tumorigenesis [24]. Whether these differences in survival are due to differential sensitivity towards anthracyclines, altered substrate-susceptibility or substrate binding-sites, or whether they can be applied to other functional and structural properties still remains unclear and needs further exploration. If chemotherapeutic agents themselves induce increased expression of transporter genes or increased transcription activity is also still a matter of investigation.

Interestingly, these polymorphisms did not confer any differences with regard to other AML specific characteristics and known risk factors for worse survival like secondary AML, white blood count, serum LDH, FLT3-ITD, or NPM1-mutation status at diagnosis. There were no differences concerning CR rates in these three MRP1 SNP patient cohorts. Though CR was not significantly affected, genotypes CC for rs129081, TT for rs212090, and GG for rs212091 predicted inferior OS and DFS. These findings are in concordance with data by Schaich et al., who demonstrated an influence of MRP1 gene expression on DFS, but not on CR [25]. Post-remission therapy had also no significant impact on outcome. Though a trend towards worse outcome and a higher incidence of relapse could be associated with MRP1 polymorphisms, validation of our data in an independent AML cohort is necessary to confirm these observations for further research.

Moreover, no significant effect of these SNPs on chemotherapy-related toxicities was seen. In contrast, Cao et al. demonstrated an association of MRP1 SNPs with gastrointestinal toxicities after chemotherapy in a Chinese population, which we could not confirm in our study of Caucasian patients [26]. No correlation was observed regarding age, gender, ECOG performance status, FAB subtypes, bone marrow blasts at diagnosis, or baseline blood count parameters (data not shown). As these three MRP1 SNPs were in allele frequency accordance to healthy Caucasian individuals (data from dbSNP), we suggest a genetic predisposition for altered chemotherapy response, therapy resistance, and worse survival. The identification of linked polymorphisms indicates the influence of certain SNP haplotypes on therapy sensitivity and outcome in AML therapy.

On a molecular level, we hypothesize these SNPs as possible causal factors for differential anthracycline
susceptibility. Therapy resistance conferred by MRP1 SNPs might be an effect dominant in relapsed or progressive disease, when sensitive AML subclones are eliminated by cytotoxic chemotherapy and resistant blasts expressing MRP1 SNPs proliferate in contrast to their chemosensitive counterparts. ABC transporter-associated MDR via drug efflux could be addressed in several studies [27, 28]. Therefore, AML patients carrying these genotypes associated with a poor prognosis may benefit from alternative therapeutic consolidation strategies like early allogeneic stem cell transplantation, higher dosages of daunorubicin, or alternative formulations of daunorubicin (e.g., CPX-351) during induction treatment [29]. Recently, higher dosages of daunorubicin during induction chemotherapy have also been demonstrated to be beneficial in certain subgroups of AML patients [30]. Therapeutic strategies trying to modulate the efflux of these transporters have failed in most clinical AML trials so far [31].

In conclusion, we demonstrate the influence of MRP1 transporter polymorphisms CG of rs129081 on DFS, rs212090 TT allelic variant on DFS, and homozygous allele expressions GG and AA of rs212091 on OS, as well as AA and AG allelic rs212091 variants on DFS in AML patients with a normal karyotype for the first time to the best of our knowledge. Hence, we suggest these SNPs to be independent prognostic markers for AML concerning survival. As SNPs in miRNA binding sites may have an effect on gene transcription and protein expression, certain SNPs influencing prognosis in AML should be evaluated in addition to established mutational changes in AML to improve prognostic algorithms and individual treatment intensity and survival of AML patients.

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Availability of data and material The datasets generated and analyzed during the study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors’ contributions Desiree Kunadt and Friedrich Stölzel performed the research. Friedrich Stölzel, Markus Schaich, and Christian Dransfeld designed the research study. Desiree Kunadt, Claudia Dill, and Maria Schmiedgen performed the experiments. All authors analyzed and interpreted the data. Desiree Kunadt and Friedrich Stölzel wrote the paper. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Consent to participate Informed consent was obtained from all patients for being included in the study.

Consent for publication All authors approved the manuscript and gave their consent for publication.

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