Clinical Significance of CD33 Nonsynonymous Single-Nucleotide Polymorphisms in Pediatric Patients with Acute Myeloid Leukemia Treated with Gemtuzumab-Ozogamicin–Containing Chemotherapy

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Abstract

**Purpose:** The purpose of this study was to evaluate clinical implications of CD33 single-nucleotide polymorphisms (SNP) in pediatric patients with acute myeloid leukemia (AML) treated with gemtuzumab-ozogamicin (GO)–based therapy.

**Experimental Design:** We genotyped four CD33 SNPs: rs35112940 (G>A; Arg304Gly), rs12459419 (C>T; Ala14Val), rs2455069 (A>G; Arg69Gly), and rs1803254 (G>C; 3’UTR) in pediatric patients undergoing induction chemotherapy containing GO (COG-AAML03P1 trial; n = 242) or not containing GO (St. Jude AML02 trial; n = 172).

**Results:** CD33 SNPs were correlated significantly with clinical characteristics and treatment outcome. The coding SNPs, rs35112940 and rs12459419, were significantly associated with clinical endpoints in COG-AAML03P1 but not in the St. Jude AML02 trial. Specifically, among white patients in COG-AAML03P1, the 3-year overall survival (OS) rate from remission was 84% ± 8% for those homozygous (GG) for rs35112940 versus 68% ± 15% for the other genotypes (P = 0.018); these patients also had a lower relapse risk and superior disease-free survival. Likewise, patients homozygous for variant allele (TT) for rs12459419 were more likely to have favorable risk disease than CC and CT genotypes (52% vs. 31%, P = 0.034) and significantly lower diagnostic blast CD33 expression than other genotypes (P < 0.001).

**Conclusion:** Our data suggest that genetic variations in CD33 could impact clinical outcome of GO-based therapy in pediatric AMLs. Clin Cancer Res; 19(6); 1620–7. ©2013 AACR.

Introduction

Acute myeloid leukemia (AML) remains a difficult-to-treat disease, and novel, efficacious therapies are needed. A promising approach includes monoclonal antibodies as specific means to deliver anti-AML therapy. The cell surface antigen currently most exploited is CD33, given its expression on AML blasts of 85% to 90% of all patients and preclinical studies indicating that ablation of CD33+ cells could eliminate leukemia in vitro and allow re-establishment of normal hematopoiesis in some cases (1).

The recognition that antibodies were internalized after binding to CD33 led to the development of gemtuzumab ozogamicin (GO, Mylotarg), an immunotoxin conjugate between an anti-CD33 antibody and a toxic calicheamicin-γ derivative (1–3). As the first cancer immunoconjugate ever to receive U.S. Food and Drug Administration (FDA) approval, GO was indicated for the treatment of CD33+ AML in first relapse for patients older than 60 years of age who were not considered candidates for conventional chemotherapy (4). This approval was based on results from interim analyses of phase II monotherapy trials showing...
CD33 SNPs as Markers of GO Response

Translational Relevance

Acute myeloid leukemia (AML) remains a difficult-to-treat disease, and novel, efficacious therapies are needed. Gemtuzumab-ozogamicin (GO), a CD33 antibody conjugated with the toxin calicheamicin, is a promising agent for AML therapy. However, there is substantial interpatient variability in clinical response to GO. In the present study, we evaluated CD33 genetic variation and our results suggest that coding polymorphisms within CD33 are significantly associated with clinical outcome in patients with AMLs receiving GO-containing chemotherapy. Integration of this information as an independent prognostic marker into current cytogenetic/molecular-based risk classification models would present an opportunity to increase our accuracy in forecasting therapeutic outcome in AMLs. This refinement would help our efforts to inform patients properly about expected treatment results and provide better-quality guidance in their decision making process. An improvement in disease risk classification would also allow more tailored, risk-stratified treatment approaches, which will be a major advancement over current strategies.

Patients and Methods

Patient samples

Cohort I. Details of COG-AAML03P1 (NCT00070174) were reported previously (8). Briefly, from 2003 to 2005, this trial enrolled 340 children (ages 1 month–21 years) with newly diagnosed de novo AMLs, excluding those with acute promyelocytic leukemia and Down syndrome. Cycle regimens were cytarabine/daunorubicin/etoposide (ADE) plus GO (induction I), ADE (induction II), high-dose cytarabine and etoposide (intensification I), mitoxantrone/cytarabine plus GO (intensification II), and sequential high-dose cytarabine and asparaginase (intensification III). Patients with matched family donor could receive SCT on study after intensification I and were not excluded or censored from the analyses. Patients who were taken off-protocol at the end of induction 1 due to marrow blasts exceeding 20% were considered an event (induction failure) for event-free survival (EFS) but were not included for analyses from the end of course 1 [disease-free survival (DFS), relapse risk (RR), treatment-related mortality (TRM)].

CD33 SNPs were determined in gDNA isolated from bone marrow aspirate specimens from patients who consented to biologic studies and had such specimens available at the end of Induction I (n = 242). Informed consent was obtained in accordance with the Declaration of Helsinki. The institutional review boards of all participating institutions approved the clinical protocol, and the COG Myeloid Disease Biology Committee approved this study.

Cohort II. Details of the St Jude AML02 study trial (NCT00136084) were described elsewhere (9). Briefly, from 2002 to 2008, 232 children with de novo AML (n = 206), therapy-related or myelodysplastic syndromes (MDS)-related AMLs (n = 12), or mixed-lineage leukemia (n = 14) were randomized to receive high-dose cytarabine (n = 113) or low-dose cytarabine (n = 117) plus daunorubicin and etoposide. Subsequent therapy was adapted on the basis of minimal residual disease (MRD) as assessed by flow cytometry and diagnostic risk features. Of 232 patients, 176 patients who did not receive GO and had specimens available were included in the present study. The Institutional review board approved the study.

Identification and genotyping of SNPs in CD33

To characterize the spectrum of frequently occurring CD33 SNPs, we sequenced the coding region of CD33 in 100 randomly selected samples from the COG-AAML03P1 cohort, using methods described previously (7). Sequencing studies identified 4 CD33 SNPs (rs12459419, rs35112940, rs2455069, and rs1803254) that occurred in 10% of specimens. These 4 SNPS were genotype in the AAML03P1 (n = 242) and the St. Jude AML02 (n = 176) cohort using the Sequenome platform at Biomedical Medical Genomics Center (BMGC) at the University of Minnesota (Minneapolis, MN).

Risk stratification

AAML03P1. A combination of cytogenetic and molecular abnormalities was used for the retrospective risk stratification for this analysis. A patient was considered favorable-risk if a chromosomal abnormality/mutation was present in core-binding factors [CBF, t(8;21) or inv(16)t(16;16)], nucleophosmin-1 (NPM1), or CEBPN. Patients were classified as high-risk if they had -5/-5q, monosomy 7, or FLT3/
ITD with high allelic ratio. All other patients with data sufficient for classification were considered standard-risk. Patients of unknown risk were those for whom cytogenetic/molecular data were insufficient for classification.

**St Jude AML02.** Patients were provisionally classified as having low-risk AML if their leukemic cells had t(8;21)/AML1-ETO, inv(16)/CBFβ-MMY11, or t(9;11)/MLL-AF9. High-risk cases included those with -7, FLT3-ITD, t(6;9), megakaryoblastic leukemia, treatment-related AMLs, or AMLs arising from MDS. All other patients were provisionally classified as having standard-risk AMLs.

**Assessment of CD33 expression**

CD33 expression on viable leukemic cells, as identified by CD45/side scatter gating properties, was prospectively quantified by multiparameter flow cytometry after staining diagnostic bone marrow specimens (AAML03P1) with CD45 and CD33 (BD Biosciences) in a centralized laboratory. Linear mean fluorescence intensity of diagnostic bone marrow specimens (AAML03P1) with quantified by multiparameter flow cytometry after staining CD45/side scatter gating properties, was prospectively classified as having CD33 expression. Indeed, we found a significant association between 3 CD33 SNPs and CD33 expression. Among 340 participants of COG-AAML03P1, 242 (71%) had DNA available from bone marrow aspirates done at end of induction I. To initially identify frequently occurring CD33 SNPs, sequencing was conducted in 100 samples that were randomly selected from these 242 specimens. A total of 8 SNPs (1 synonymous and 7 nonsynonymous) were identified in the coding region, one each in a splice site (intron 6) and in 3’-untranslated region (UTR, Table 1). All but one of these SNPs has been reported earlier (bib3). Of these 10 SNPs, 4 SNPs had a minor allele frequency (MAF) of >10% (rs12459419, rs35112940, rs2455069, and rs1803254) and were selected for further analysis. Three of these were missense SNPs, resulting in a change in amino acid, and one (rs1803254) was located in the 3’-UTR (Table 1).

**Statistical analysis**

The significance of observed differences in proportions was tested using the \( \chi^2 \) test and Fisher exact test when data were sparse. The Kruskal–Wallis test was used to determine the significance between differences in medians. The Kaplan–Meier method was used to estimate overall survival (OS), EFS, and DFS. OS was defined as time from study entry or from end of course 1 for patients in complete remission (CR) to death. EFS was defined as time from study entry until death, failure to achieve remission during induction therapy, or relapse. DFS was defined as time from end of course 1 for patients in CR until relapse or death. Relapse-free survival (RFS) was defined as the time from end of course 1 for patients in CR until relapse or death due to progressive disease where deaths from nonprogresive disease were censored. Estimates of relapse risk (RR) and TRMs were obtained using methods that account for competing events. RR was defined as time from end of course 1 for CR patients to relapse where deaths from nonprogressive disease were considered competing events. Within the AAML03P1 cohort, 5 patients died by the end of course 1; however, none of these were included in this analysis hence TRM during induction 1 was not included. Rather TRM was defined as time from end of course 1 for CR patients to death from nonprogressive disease where relapses were considered competing events. The significance of observed differences in proportions was tested using the \( \chi^2 \) test and Fisher exact test when data were sparse. The Kruskal–Wallis test was used to determine the significance between differences in medians. The Kaplan–Meier method was used to estimate overall survival (OS), EFS, and DFS. OS was defined as time from study entry or from end of course 1 for patients in complete remission (CR) until death. EFS was defined as time from study entry until death, failure to achieve remission during induction therapy, or relapse. DFS was defined as time from end of course 1 for patients in CR until relapse or death. Relapse-free survival (RFS) was defined as the time from end of course 1 for patients in CR until relapse or death due to progressive disease where deaths from nonprogresive disease were censored. Estimates of relapse risk (RR) and TRMs were obtained using methods that account for competing events. RR was defined as time from end of course 1 for CR patients to relapse where deaths from nonprogressive disease were considered competing events. Within the AAML03P1 cohort, 5 patients died by the end of course 1; however, none of these were included in this analysis hence TRM during induction 1 was not included. Rather TRM was defined as time from end of course 1 for CR patients to death from nonprogressive disease where relapses were considered competing events. The significance of predictor variables was tested with the log-rank statistic for OS, EFS, DFS, and with Gray’s statistic for RR and TRM. Clinical outcome data were analyzed through November 18, 2010. Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months before November 18, 2010. Cox proportional hazard models were also used to estimate HRs with 95% confidence intervals (CI) for univariate and multivariate analyses.

**Results**

**CD33 SNPs in COG-AAML03P1 and St. Jude AML02**

Among 340 participants of COG-AAML03P1, 242 (71%) had DNA available from bone marrow aspirates done at end of induction I. To initially identify frequently occurring CD33 SNPs, sequencing was conducted in 100 samples that were randomly selected from these 242 specimens. A total of 8 SNPs (1 synonymous and 7 nonsynonymous) were identified in the coding region, one each in a splice site (intron 6) and in 3’-untranslated region (UTR, Table 1). All but one of these SNPs has been reported earlier (bib3). Of these 10 SNPs, 4 SNPs had a minor allele frequency (MAF) of >10% (rs12459419, rs35112940, rs2455069, and rs1803254) and were selected for further analysis. Three of these were missense SNPs, resulting in a change in amino acid, and one (rs1803254) was located in the 3’-UTR (Table 1).

**Association between CD33 SNPs and CD33 expression in COG-AAML03P1**

Quantitative data on CD33 expression were available from 222 (91.7%) of the 242 patients from COG-AAML03P1. As expression of CD33 has recently been linked to clinical outcome (11), we wondered about a relationship between CD33 SNPs and CD33 expression. Indeed, we found a significant association between 3 CD33 SNPs and CD33 expression on AML blasts. As shown in Fig. 1, patients homozygous for the reference allele (AA) of the SNP, rs2455069 (A>G; Arg69Gly), had a significantly lower median CD33 expression than those with either AG or AA genotype (AA vs. AG vs. GG: 90.2 vs. 144.4 vs. 166.6 respectively; \( P = 0.022 \)). rs2455069 also occurs in linkage disequilibrium (LD) with a promoter SNP rs386544. Furthermore, SNP rs12459419 (C>G; Ala14Val) and the 3’-UTR SNP rs1803254 (C>G) were both associated with lower median CD33 expression (rs12459419; CC vs. CT vs. TT; 152.2 vs. 97.4 vs. 44.8; \( P < 0.001 \) and rs1803254: GG vs. CT vs. CC; 146.1 vs. 94.7 vs. 46.4; \( P = 0.029 \)). rs35112940 SNP that results in coding change was not associated CD33
expression levels in the diagnostic leukemic blasts (AA vs. AG vs. GG; 39.6 vs. 99.2 vs. 139.1; \(P = 0.39\); Fig. 1).

### Association of CD33 SNPs with clinical outcome

Finally, we evaluated clinical outcome data for the various genotypes of each SNP (Table 2); due to the varying prevalence of the SNPs across different races, clinical outcomes were also compared separately for African Americans and Caucasians. For SNPs rs35112940, rs12459419, and rs1803254 but not rs2455069, our analyses indicated significant associations with clinical outcome as follows.

**SNP rs35112940.** Relative to patients with the GG genotype, those with variant alleles (AA and AG genotypes) had a significantly higher RR (48% ± 14% vs. 29% ± 7%; \(P = 0.019\)). As rs35112940 was predominantly present in Caucasians (MAF = 0.16) and was quite rare in African Americans (MAF = 0.01), we restricted further analyses to Caucasian patients. As shown in Fig. 2A, OS from end of course 1 for patients with variant allele (genotype AA and AG, \(n = 40\)) was significantly worse than for those with the GG genotype (\(n = 101\); 68% ± 15% vs. 84% ± 8%; \(P = 0.036\)). OS from study entry followed a similar trend but did not reach statistical significance (67% ± 14% vs. 78% ± 8% for AA + AG vs. GG; \(P = 0.09\)).

Consistently, patients carrying variant allele (AA + AG) for rs35112940 had the higher RR than those with the

### Table 1. CD33 SNPs identified by sequencing and genotyped in the present study

<table>
<thead>
<tr>
<th>CD33 SNP</th>
<th>rs#</th>
<th>Location</th>
<th>Allele frequency</th>
<th>Flanking sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu10Leu</td>
<td>rs117255828</td>
<td>Exon 1</td>
<td>T = 0.02</td>
<td>GCTGCCCTTG-C-TGTGGGCAGG</td>
</tr>
<tr>
<td>Ala14Val</td>
<td>rs12459419</td>
<td>Exon 2</td>
<td>T = 0.31</td>
<td>CCCACAGGGG-C-CCTGGCTATG</td>
</tr>
<tr>
<td>Arg62Glu</td>
<td>Exon 2</td>
<td>A = 0.005</td>
<td>TACTGTTCC-G-GAAAGGAGCC</td>
<td></td>
</tr>
<tr>
<td>Ala65Pro</td>
<td>Exon 2</td>
<td>C = 0.005</td>
<td>CGGGAAAGGA-G-CCATTATAC</td>
<td></td>
</tr>
<tr>
<td>Arg69Gly</td>
<td>rs2455069</td>
<td>Exon 2</td>
<td>G = 0.4</td>
<td>CCATTATATCC-A-GGAGCTCTCC</td>
</tr>
<tr>
<td>Phe243Leu</td>
<td>rs11882250</td>
<td>Exon 4</td>
<td>C = 0.01</td>
<td>AACTGTTATC-T-TTCCAGGAGGA</td>
</tr>
<tr>
<td>Val267Ile</td>
<td>rs58981829</td>
<td>Exon 5</td>
<td>A = 0.02</td>
<td>AGGAAGCTGTC-G-CTACAGCCT</td>
</tr>
<tr>
<td>Arg304Gly</td>
<td>rs35112940</td>
<td>Exon 6</td>
<td>A = 0.13</td>
<td>CTCCTACACA-G-GGTGAGCCTC</td>
</tr>
<tr>
<td>Ser305Pro</td>
<td>rs61736475</td>
<td>Exon 6</td>
<td>C = 0.04</td>
<td>TACCAAGGGG-C-CAGCCTCCCC</td>
</tr>
<tr>
<td>Ala331Thr</td>
<td>rs35632246</td>
<td>Exon 7</td>
<td>G = 0.004</td>
<td>TGCCGCCCTCC-A-CTGGAGAT</td>
</tr>
<tr>
<td>intron 6</td>
<td>rs273621</td>
<td>Intron 6 (splice site)</td>
<td>C = 0.01</td>
<td>GCCTCCCGGG-T-GAGTGAATG</td>
</tr>
<tr>
<td>3' UTR</td>
<td>rs1803254</td>
<td>3' UTR</td>
<td>C = 0.22</td>
<td>CATTGCTAAG-G-TGTATGAGT</td>
</tr>
</tbody>
</table>

**NOTE:** SNPs in bold occur with MAF of more than 0.1 were selected for genotyping.
CG genotype (45% ± 16% vs. 24% ± 8%; AA + AG vs. GG; $P = 0.018$; Fig. 2B and Table 2). Furthermore, DFS from the end of course 1 was marginally lower in patients homozygous for variant allele than in patients with at least one G allele (66% ± 8% vs. 33% ± 39%; $P = 0.05$; Table 2).

**SNP rs12459419.** A trend toward better 3-year OS from study entry was observed for patients homozygous with TT genotype as compared with patients having at least one C allele (CC + CT) genotype (88% ± 13% vs. 69% ± 6%; $P = 0.056$).

**SNP rs1803254.** Patients with at least one variant allele (CC + CG) had a 3-year TRM of 13% ± 12% compared with 3% ± 3% for patients wild-type allele (GG; $P = 0.027$; Fig. 3).

Multivariate analyses using Cox regression models were conducted for OS, EFS from study entry as well as OS, DFS, and RFS from end of course 1 for patients with rs12459419.
rs35112940, and rs1803254 SNPs separately. After adjusting for race (white vs. not white) and risk group (standard, favorable, high), in multivariate analyses, rs35112940 SNP retained significance for RFS (HR, 1.91; 95% CI, 1.10–3.32; \( P = 0.022 \)). Additional multivariate analyses including adjustments for WBC (<50k vs. \( \geq 50k \)) yielded similar results.

We also evaluated association of CD33 SNPs (rs35112940, rs12459419, and rs1803254) in 176 patients enrolled on St. Jude AML02 study who did not receive GO as part of their chemotherapy. Compared with COG-AAML03P1, participants on this trial were relatively similar with regard to gender, age, race, cytogenetics, and FLT3 status (all \( P > 0.1 \)). Equally comparable were allele frequencies of these CD33 SNPs (15% vs. 19% for rs1803254; 15% vs. 13% for rs35112940, and 28.2% vs. 28.7% for rs12545919 in St. Jude AML02 and COG-AAML03P1, respectively). None of the CD33 SNPs showed significant association with clinical outcome (MRD day 22, OS, DFS, RFS, or RR) within this cohort (results for rs35112940 are shown in Fig. 4A and B).

### Discussion

In this study, we evaluated 3 nonsynonymous coding SNPs and one 3′-UTR SNP in CD33 for their association with disease features and outcomes of intensive chemotherapy in pediatric AMLs. We found that several SNPs were significantly associated with outcome in patients who received GO-containing therapy but not in those who did not receive GO, suggesting that CD33 SNPs impact clinical response to GO.

The long-term goal of pharmacogenetic studies such as ours is to use genotype data to predict beneficial or adverse response to specific drug and then use this information to optimize the drug’s therapeutic efficacy and minimize its toxicity by helping in the selection of appropriate patient subsets.

Emerging clinical data from several studies now indicate that GO might be efficacious for subgroups of AMLs (5, 6, 12, 13). Pharmacogenetic information may thus be particularly useful for a drug such as GO, which has been shown to provide important benefit for some patients with AMLs but is ineffective in others, in which it may only lead to increased TRM. Given this significant interpatient variation in response, the drug’s benefit may be missed if used in unselected patients. In fact, the lack of benefit of GO across the entire study population of the Southwest Oncology Group S0106 trial and the slightly higher TRM observed in this study led the manufacturer of GO to withdraw commercial drug availability in the United States in 2010 (1, 14). We analyzed association of CD33 SNPs with clinical outcome measures both from entry and end of course 1 and found most significant association from end of induction 1. By identifying CD33 SNPs that are associated with response to GO-containing therapy, in particular SNP rs35112940—which we found associated with lower OS, DFS, and higher RR from the end of course 1—our data suggest that pharmacogenetic information might be useful to individualize the use of GO in the clinic.

The potential molecular mechanisms underlying the observed associations between CD33 SNPs and CD33...
expression and/or clinical outcome are currently unclear and under active investigation. However, as the rs35112940 SNP results in an amino acid substitution close to the ITIM motif in CD33, it is tempting to speculate that this SNP could impact the formation of a CD33–GO complex or the rate of its internalization. On the other hand, rs12459419 SNP that was significantly associated with CD33 expression results in an amino acid change in the signal peptide in CD33, which may interfere with protein trafficking and cell surface expression of CD33 molecules. In pediatric patients with AMLs receiving GO as part of a multi-agent therapy, higher CD33 expression has been shown to be associated with high-risk disease (FLT3/ITD + disease, high-risk cytogenetics, e.g., -7, -5, -5q; ref. 11). This SNP was also more frequent in patients within favorable risk group in AAML03P1 cohort but not in AML02 cohort, the reason for this discrepancy is not clear. While the risk classifications of the 2 protocols were similar, they were not identical and it is not possible to fully reconcile the risk classifications of the 2 protocols because they each measure some molecular characteristics that were not captured on the other protocol. Future work to define the interplay between CD33 SNP, CD33 expression, and risk group is needed to understand the molecular mechanism responsible for this observation.

A major limitation of our study is that the conclusion that clinical impact of CD33 SNPs is limited to GO is based on a comparison of data from 2 independent clinical trials (COG-AAML03P1 and St. Jude AML02). It is theoretically possible that CD33 and CD33 SNPs can impact response to non-CD33–targeted chemotherapy. In fact, although the biologic role of CD33 remains obscure, CD33 has been implicated in cellular proliferation and survival of AML cells (15); thus, more global effects of CD33 SNPs need to be considered. Another major limitation is that we conducted a large number of comparisons which can increase the likelihood of a false-positive result. Therefore, further validation of our findings is critical. To this end, our future studies are targeted toward evaluation of COG-AAML0531, a phase III trial of more than 1,000 patients in which the value of GO addition to intensive chemotherapy was studied in a randomized fashion. This will allow a direct assessment as to whether the association between outcome and CD33 SNPs is limited to GO, as our data indicate.

In conclusion, our findings suggest that CD33 SNPs identified in the gDNA are associated with clinical features of AMLs and outcome after GO-containing combination chemotherapy in patients with AMLs. If these data are confirmed, CD33 SNPs could serve as prognostic markers and to help in the selection of patient subsets most suitable for therapies containing GO and possibly other CD33-targeted immunotoxins in future prospective trials.

Disclosure of Potential Conflicts of Interest

R.B. Walter received research funding from and has an advisory and consultant role at Seattle Genetics Inc. J. Franklin is employed in a leadership position, has stocks, and obtained research funding at Amgen Inc. M.R. Loken is funded by and employed in a leadership position at Hematologies Inc. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Mortland, A.K. Mitra, J.A. Pollard, M.R. Loken, S. Raimondi, J. Franklin, J.E. Rubnitz, A. Gamis, J.K. Lamba.


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Raimondi, S. Pounds, S. Meshinchi, J.K. Lamba.

Study supervision: A. Gamis, J.K. Lamba.

Reviewed cytogenetics data used in determining risk classification: B. Hirsch.

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