Integrated Genomic Profiling, Therapy Response, and Survival in Adult Acute Myelogenous Leukemia

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Abstract

Purpose: Recurrent gene mutations, chromosomal translocations, and acquired genomic copy number aberrations (aCNA) have been variously associated with acute myelogenous leukemia (AML) patient outcome. However, knowledge of the co-occurrence of such lesions and the relative influence of different types of genomic alterations on clinical outcomes in AML is still evolving.

Experimental Design: We performed SNP 6.0 array-based genomic profiling of aCNA/copy neutral loss-of-heterozygosity (cnLOH) along with sequence analysis of 13 commonly mutated genes on purified leukemic blast DNA from 156 prospectively enrolled non-FAB-M3 AML patients across the clinical spectrum of de novo, secondary, and therapy-related AML.

Results: TP53 and RUNX1 mutations are strongly associated with the presence of SNP-A-based aCNA/cnLOH, while FLT3 and NPM1 mutations are strongly associated with the absence of aCNA/cnLOH. The presence of mutations in RUNX1, ASXL1, and TP53, elevated SNP-A-based genomic complexity, and specific recurrent aCNAs predicted failure to achieve a complete response to induction chemotherapy. The presence of ≥1 aCNA/cnLOH and higher thresholds predicted for poor long-term survival irrespective of TP53 status, and the presence of ≥1 aCNA/cnLOH added negative prognostic information to knowledge of mutations in TET2, IDH1, NPM1, DNMT3A, and RUNX1. Results of multivariate analyses support a dominant role for TP53 mutations and a role for elevated genomic complexity as predictors of short survival in AML.


Introduction

Substantial progress has been made in the characterization of recurrent genomic aberrations in acute myelogenous leukemia (AML) and their association with clinical outcomes. In particular, risk groups of AML based on karyotype-based cytogenetics remain important in daily clinical decision-making (1–3). Over the last few years, several groups have extended the discovery of multiple recurrently mutated protein-coding genes in AML by reporting the prognostic and therapeutically predictive significance of individual mutations [including NPM1 (4–6), FLT3 (7–9), CEBPA (10, 11), DNMT3A (12–14), RUNX1 (15–17), TET2 (18, 19), ASXL1 (20, 21), IDH1 (22, 23), IDH2 (24, 25), NRAS/KRAS (26, 27), TP53 (28–30), and others (31–34)] as well as combinations of these mutations (35–38) in AML patient cohorts. In addition, several groups have published studies demonstrating the correlation of specific SNP array-detected aCNA or the total number of aCNA/cnLOH (genomic complexity) with clinical outcomes (29, 39–43). Importantly, however, the relative influence on clinical AML outcomes of different types of genomic alterations, including gene mutations, structural genomic changes, or aCNA/cnLOH, remains unclear as lesion types rarely occur in isolation. While a few integrated analyses of the patterns of co-occurrence of various genomic alterations have been published (44), these studies have not extended findings to the study of chemoresistance and survival.

A majority of studies assessing the prognostic value of mutated genes in AML have been restricted to AML with normal karyotype (NK-AML), as this category is clinically heterogeneous, lacks a prognostic structural genomic marker, and because some mutated genes are enriched in NK-AML. The published cohorts studied often are selected on the basis of clinically derived classifications of AML subgroups, including secondary AML (sAML) that arises in the setting of an antecedent myeloid neoplasm, and de novo AML (dnAML) that presents without a history of either previous therapy or a preexisting myeloid neoplasm. As many of these studies are based on cohorts of patients enrolled in therapeutic trials, they are subject to selection based on age and other inclusion and exclusion criteria, which adds further restrictions on the population analyzed.
Translational Relevance

Several gene mutations, structural chromosomal aberrations, specific acquired copy number aberrations (aCNA), and the total number of aCNAs as detected through SNP 6.0 array profiling have been associated with clinical outcome in acute myelogenous leukemia (AML). However, it remains incompletely understood how their interrelatedness affects their predictive and prognostic usefulness. In an AML cohort, failure to achieve a complete remission after one or two intensive induction regimens predicted for very poor long-term survival. The partial or complete resistance to induction chemotherapy significantly associated with mutations in RUNX1, ASXL1, and TP53, various recurrent aCNAs, and elevated SNP–A–based genomic complexity. Prognostically, the presence of ≥1 SNP–A–based aCNA/cnLOH and all higher thresholds predicted for poor long-term survival irrespective of TP53 status. When combining these data with AML-TCGA results in de novo AML, the presence of ≥1 aCNA/cnLOH added negative prognostic information to knowledge of mutations in TET2, IDH1, NPM1, DNMT3A, and RUNX1.

To further refine basic biologic knowledge of patterns of occurrence of genomic lesion types in AML and of the effects of various genomic aberration types on AML outcome, we profiled a consecutively enrolled prospective AML cohort for aCNA/cnLOH using SNP 6.0 array profiling and determined the mutation status of 13 recurrently mutated genes using Sanger sequencing. This approach has allowed us to integrate multiple genomic features across all major clinical subgroups of non-M3 AML and across the full age range of adult patients. Here, we identify genomic traits that associate with clinical AML subtypes, gene mutations that associate with genomic complexity or stability, and genomic traits that associate with sensitivity or resistance to standard induction therapy and ultimately survival.

Materials and Methods

Patients

Between March 2005 and June 2011, 173 patients with previously untreated non-M3 AML were enrolled into this study at the University of Michigan Comprehensive Cancer Center (Ann Arbor, MI). The study was approved by the University of Michigan Institutional Review Board (IRBMED #2004-1022) and written informed consent was obtained from all patients before enrollment. Of the samples from 173 patients, 156 resulted in aCNA/cnLOH.

Array data analysis

Affymetrix CEL files for each blast and buccal sample underwent initial quality control screening with the Genotyping Console program after which Affymetrix “Birdseed” algorithm generated SNP call files with call rates for the entire sample group between 93.64% and 99.45%, with a mean call rate of 98.17%; none gave out-of-bounds results.

Genomic copy number heatmaps were generated as previously described (45). Two independent observers visually inspected parallel heatmap copy number images of AML blast and paired normal DNA samples generated through dChip. Only those copy number changes detected in blast DNA but not in paired normal DNA were called somatic, and lesions had to be ≥30 SNP positions in length to be scored positive. All visually determined aCNA were corroborated with an algorithmic lesion calling method as previously described (47). LOH analysis was performed using LOH tool v2 as previously described (29). All resulting aCNA/cnLOH are listed in Supplementary Table S3 and SNP 6.0 array data files for all 156 patient samples analyzed were deposited in the GEO public database (accession number GSE61323).

TCGA data analysis

The recently published AML cohort of The Cancer Genome Atlas (TCGA) provided additional clinically annotated gene mutation and SNP–A–patient data (44). To facilitate a meaningful comparison of aCNA/cnLOH from TCGA with the Michigan cohort, SNP 6.0 Affymetrix CEL files from paired normal and
tumor TCGA AML specimens were downloaded from dbGaP after obtaining data access approval (dbGaP approval #29753-3). These files were analyzed with the identical informatics preprocessing pipeline and visual and algorithmic lesion calling methods used for the Michigan SNP 6.0 arrays above.

Of the 200 published matched pairs, twenty were excluded due to a diagnosis of APL (AML-M3), two for out-of-bounds results (TCGA-2855 and -2883), two for failure to pass the "Birdseed" algorithm (TCGA-2848 and -2981), and six for high visual and algorithmic background noise that precluded accurate lesion calling (TCGA-2802, -2833, -2843, -2847, -2876, and -2891). This resulted in 170 matched pairs with a complete catalog of aCNA/cnLOH, which is included in Supplementary Table S3. Gene mutation status for the thirteen genes of interest in this study and clinical characteristics including survival data based on the May 13, 2013, update were obtained from published Supplementary Data (44). Notable differences in the genomic profiling of TCGA specimens compared with the Michigan cohort include the use of whole exome or genome sequencing followed by non–Sanger based confirmation of gene mutation status and the use of tumor samples that were not enriched for leukemic cells.

Statistical analysis

Overall survival was defined as time (in months) between AML diagnosis and the patient’s death. For patients still alive, the censoring date was September 1, 2013. Univariate and bivariate analyses were based on Kaplan–Meier estimates of survivor functions. Median survival times were estimated directly from the survivor function estimates. Significance levels for group-wise comparisons in the univariate analyses assess whether the HR between groups differs from 1 in a Cox proportional hazards model. For bivariate analyses, Cox models were fit to subsamples defined by the levels of one of the two factors being analyzed. The reported P value assesses whether the univariate HR for the other factor differs from 1 within the subsample. Multivariate analyses on Cox proportional hazards models with additive effects for the factors as reported in the results. The reported significance levels assess whether the hazard for a given factor differs from 1 when the other factors in the model are held fixed.

Comparison of clinical features of the various groups studied was performed using two-sided χ², Mann–Whitney, and Kruskal–Wallis tests. Pairwise associations between gene mutations, recurrent aCNA/cnLOH, etiological AML subtypes, and type of response to induction chemotherapy were calculated using a two-sided Fisher exact test corrected for multiple hypotheses testing with the Benjamini–Hochberg FDR algorithm and denoted using q values. The SEM was calculated for the mean number of aCNA/cnLOH associated with each mutated gene.

Results

Patient characteristics

Characteristics of the 156 prospectively enrolled, previously untreated, non-M3 FAB subtype AML patients (referred to hereafter as the “MI-All-AML” group) in this study are summarized in Supplementary Tables S1 and S2. Of the 156 patients, 114 underwent SNP-A analysis and limited gene sequencing in a previously published study (29). Sixty-six percent, 22%, and 12% of cases were dnAML, sAML, or tAML, respectively, and 35% (54/156) of cases had normal cytogenetics. Within the dnAML group, 17% had a recurrent genomic abnormality, 19% had myelodysplasia-related changes without a history of an antecedent myeloid neoplasm, and 64% were diagnosed as AML-not-otherwise-specified. Forty-two percent (43/103) of dnAML cases had normal cytogenetics. Regarding therapy, 93%, 66%, and 78% of dnAML, sAML, and tAML cases, respectively, received high-intensity induction chemotherapy, and 30% (47/156) underwent allogeneic stem cell transplantation while in complete remission, 45% (21/47) of whom were alive >3 years after diagnosis. Seventy-six percent (119/156) of patients had died at the time of data analysis, and median follow-up for surviving patients was 57.4 months.

Clinical characteristics of the AML TCGA cohort are published elsewhere (44). Of note, the TCGA dataset comprises only dnAML cases and is compared in this study with the dnAML subgroup of Michigan cases (hereafter referred to as the "TCGA-dnAML" and "MI-dnAML" groups, respectively). The clinical features of the TCGA-dnAML and MI-dnAML groups are well matched with the exception of the fractions receiving high-intensity treatment (79% vs. 93%, respectively; P < 0.01). The comparison of these two groups is summarized in Supplementary Table S1.

Mutational spectrum of thirteen genes across clinical AML subsets

Mutation frequency of 13 recurrently mutated genes is summarized in Fig. 1A. Eighty percent (125/156) of cases had a mutation in at least one of these genes. IDH2 (19% vs. 3%), NPM1 (24% vs. 3%), and FLT3 (21% vs. 11%) mutations were enriched in dnAML compared with sAML (P ≤ 0.05 for all), while IDH1 (17% vs. 8%), ASXL1 (26% vs. 13%), and TP53 (26% vs. 8%) mutations were overrepresented in sAML compared with dnAML (P ≤ 0.05 for all). For tAML, 50% (9/18) of cases harbored mutant TP53 (Fig. 1B). ASXL1 occurred more frequently in patients ≥60 years old (P = 0.05) due to the increased proportion of sAML in that population; however, comparing age ≥60 to age <60 in the dnAML group alone showed enrichment of RUNX1 and TET2 in older patients (both 22% vs. 7%, respectively; P < 0.05), while the remaining eleven genes showed no significant difference in mutation frequency. Co-occurrence analysis of mutations in all AML cases demonstrated mutual exclusivity of TP53 and RUNX1, NPM1 and RUNX1, and IDH1 and IDH2 (Fig. 1A). A detailed catalog of gene mutations for each case is included in Supplementary Table S4. Mutation frequency in these subgroups was consistent with published data with the exception of ASXL1 in dnAML (13% vs. 3%) (36, 44) and TP53 in tAML (50% vs. 18%–21%; refs. 48, 49).

Topography of aCNA and cnLOH

A total of 455 copy number losses, 106 copy number gains, and 38 instances of cnLOH were identified, with 20% <1 Mb and 47% <5 Mb (Supplementary Table S3). aCNA/cnLOH were common in the MI-All-AML group with 62% (97/156) of cases harboring ≥1 lesion and 38% (59/156) of cases with ≥2 lesions (median 2, range 1–39); similar findings were noted in the dnAML subgroup with ≥1 lesion seen in 56% (58/103) of cases and ≥2 lesions in 29% (30/103) of cases (median 2, range 1–25). In addition, aCNA/cnLOH were detected in 31% (17/55) of cases with a normal karyotype. In cases with abnormal karyotype, additional SNP-A lesions not detected by karyotype were found in 51% of cases (53/102). The average number of copy number losses (1.6 vs. 4.4 vs. 7.7) as well as total aCNA/cnLOH (2.2 vs. 6.4 vs. 8.6)
de overlapping aCNA/cnLOH, the boundaries of the MADR were determined by first identifying genomic regions in which aCNA/cnLOH occurred in ≥5% of cases. For each of these overlapping aCNA/cnLOH, the boundaries of the MADR were defined by the genomic interval containing the peak number of involved cases. For large regions multiple MADR were permitted if the peak number of involved cases decreased by ≥2. MADR were identified on chromosomes 3p, 5q, 6p, 7, 8, 11q, 12p, 13q, 16q, 17p, 17q, 18q, and 21 and were listed in Supplementary Table S4. Deletions of the distal half of 13q14.2 as well as trisomy 21 were enriched in sAML, while deletions of 5q, 7p, 7q, 16q, 17q, 18q, and CNLOH of 17p were enriched in tAML (Fig. 1D). Associations of gene mutations with aCNA/cnLOH

Mutation status and aCNA/cnLOH were analyzed for each case. Notably, co-occurrence of a gene mutation with an aCNA/cnLOH that produced a hemizygous or homozygous mutant state at that gene’s locus was uncommon. Occasional cases with co-occurring mutations and aCNA/cnLOH. The exception was the presence of 17p deletions and CNLOH involving the TP53 locus [27% (7/26) of TP53-mutant cases with 17p deletions and 35% (9/26) of TP53-mutant cases with 17p CNLOH].

Examining the association of gene mutations with each MADR revealed significant association between KRAS and trisomy 8 (q = 0.04), BCORL1 and trisomy 21 (q = 0.01), and TP53 with all recurrent aCNA/cnLOH except for 6p−, 11q−, 13q+, 21+, and 21q−. Associations of gene mutations with SNP-A-based genomic complexity

Comparison of SNP-A–based genomic lesion loads in the MI-All-AML, MI-dnAML, or a combined dnAML (MI-dnAML and TCGA-dnAML) group further subdivided by individual gene mutations and organized by fraction of cases with 0, 1, 2, 3, 4, 5–10, and >10 aCNAs showed multiple interesting findings: (i) distinctly high genomic complexity in TP53-mutated cases (mean 15.5, SEM 2.1); (ii) low or no complexity in cases carrying IDH1, FLT3, NPM1, or CEBPA mutations; (iii) >50% of cases with mutations in BCORL1, KRAS, RUNX1, NRAS, TET2, DNMT3A, ASXL1, or IDH2 harbored ≥1 aCNA/cnLOH (Fig. 2A), and, (iv) AML cases without mutations in the 13 genes analyzed here were quite complex. In the MI-All-AML group, TP53 mutations were strongly associated with the presence of aCNA/cnLOH and NPM1 mutations with their absence (q < 0.01 for both), while in the pooled dnAML group TP53 and RUNX1 mutations were strongly associated with the presence of aCNA/cnLOH and NPM1 and FLT3 mutations with their absence (q < 0.01 for all).

A parallel analysis was performed on TP53 wild-type cases; in this group, a subset of cases within each mutation-carrying subgroup still carried high lesion loads (Fig. 2B) and substantial differences existed in the fraction of cases that carried no lesions. Specifically, in the pooled dnAML group, RUNX1 mutations remained strongly associated with the presence of aCNA/cnLOH and NPM1 and FLT3 mutations remained strongly associated with their absence (q < 0.01 for all). In both the TP53 any and...
TP53 wild-type analyses, the majority of cases with BCORL1 and KRAS mutations also contained aCNA/cnLOH and almost all cases of CEBPA lacked aCNA/cnLOH; however, the lower number of cases with these mutations precluded statistically significant associations.

Association of gene mutations, aCNA/cnLOH and karyotype with refractory AML

Within the total cohort (MI-All-AML), 132 patients received full-intensity induction chemotherapy; of these, 13 patients died during cycle one of induction chemotherapy and one declined further treatment and these patients were excluded from subsequent analysis. Of the remaining 118 patients, 65% (76/118) achieved a morphologic complete remission (CR) after one cycle of therapy (referred to hereafter as the "sensitive" group), 15% (18/118) achieved a CR after two cycles of therapy (the "intermediate" group), and 20% (24/118) failed to achieve a CR after at least two cycles of therapy (the "refractory" group).

Univariate analysis of the 118 patients examining the effect of response to induction therapy on median OS demonstrated a significant and profound difference in outcome between the sensitive, intermediate, and refractory groups (median OS of 25.8, 12.5, and 4.2 months, respectively; \( P < 0.03 \) for all; Fig. 3A).

This profound survival difference prompted evaluation of genomic features associated with these distinct responses to therapy. All cases with CEBPA biallelic mutations, t(8;21), inv(16), and any 11q23 abnormality \( (N = 3, 5, 6, \text{ and } 4, \text{ respectively}) \) were sensitive to treatment. NPM1 mutations and the absence of any aCNA/cnLOH were highly associated with the sensitive group \( (q < 0.001 \text{ for both}) \). RUNX1 mutations, on the other hand, were the only genomic feature highly associated with the intermediate group \( (q < 0.001) \). TP53 mutations \( (q < 0.001) \); SNP-A detected deletions of 3p, 5q, 7p, 7q, 12q, 16q, 17p, and 17q \( (q < 0.05 \text{ for all}) \); the presence of \( \geq 2 \) or \( \geq 3 \) aCNA/cnLOH \( (q = 0.01 \text{ and } q < 0.001, \text{ respectively}) \); and monosomal (MK) or complex karyotype \( (CK; q < 0.001 \text{ for both}) \) were all associated with the refractory group. The frequency of all measured genomic features in each response group is displayed in Fig. 3B.

Given the dominant correlation of TP53 mutations with refractory disease, MK, CK, and aCNA/cnLOH lesion load, the TP53 wild-type fraction \( (N = 105) \) was evaluated in a similar fashion. NPM1 mutations and the absence of aCNA/cnLOH remained highly associated with the sensitive group \( (q < 0.02) \) and RUNX1 mutations with the intermediate group \( (q < 0.001) \). SNP-A–based deletions of 5q, 7q, 12p, and 16q still correlated with a decreased response to therapy but were associated with the intermediate group \( (q < 0.05 \text{ for all}) \) rather than the refractory group. ASXL1 mutations emerged as significantly associated with the refractory group \( (q < 0.05) \) as well as cases with \( \geq 2 \) aCNA/cnLOH \( (q < 0.02) \). The frequency of all measured genomic features in the TP53 wild-type group is shown in Fig. 3C. Additional representations of genomic lesion frequency within specific types of therapy response are shown in Supplementary Fig. S1.

Age, cytogenetics, and gene mutations and survival in the AML cohorts studied

In the MI-All-AML group, median overall survival (OS) for age \( \geq 60 \) (6.5 months) versus age \( < 60 \) (24.0 months) and for favorable (not reached) versus intermediate (14.0 months) versus unfavorable (4.3 months) cytogenetics were significantly different \( (P < 0.01 \text{ for all}) \). Likewise, in the MI-dnAML-only subgroup, the median OS for age \( \geq 60 \) (8.4 months) versus age \( < 60 \) (26.3
Figure 3.
Genomic lesion associations with response to induction chemotherapy. Univariate analysis of median overall survival in the MI-All-AML (N = 156) and MI-dnAML (N = 103) subgroups based on type of response to therapy (A). Frequency of gene mutations and structural genomic aberrations, minimally amplified or deleted regions, and aCNA/cnLOH load stratified by response to treatment in (B) all cases or in (C) TP53 wild-type cases only.
A combined analysis of gene mutations and SNP-A–detected aCNA/cnLOH on survival in AML

As mutational profiling is increasingly employed for clinical risk stratification, we assessed the prognostic value of knowledge of aCNA/cnLOH counts in AML patients stratified by individual...
Figure 5.
Bivariate analyses of gene mutations and aCNA/cnLOH. Bivariate analyses of the effect of gene mutation status combined with the presence or absence of aCNA/cnLOH on median overall survival in the pooled Mi-dnAML and TCGA-dnAML groups ($N = 273$).
The presence of ≥1 aCNA/cnLOH in patients with mutations in TET2, IDH1, NPM1, or DNMT3A significantly worsened survival as compared with lack of aCNA/cnLOH, with similar trends detected in patients carrying RUNX1 or FLT3 mutations (Fig. 5). For example, median survival was 6.6 months versus 29.4 months in patients with TET2 mutations and presence or absence of aCNA/cnLOH, respectively (P < 0.01), and 12.9 months versus 56.3 months for patients with IDH1 mutations and presence or absence of aCNA/cnLOH, respectively (P = 0.01).

Multivariate survival analyses of age, cytogenetics, SNP 6.0 array-based genomic complexity, and gene mutations in AML

Multivariate analysis was performed using a Cox proportional hazards model of single variables in combination with age and cytogenetic risk group. For the MI-All-AML group, increased genomic complexity defined as ≥4 SNP-A lesions demonstrated a strong, independent negative impact on overall survival [HR = 1.98; 95% confidence interval (CI), 1.20–3.28; P < 0.01] with ≥3 SNP-A lesions tending toward an independent negative effect as well (HR = 1.57; 95% CI, 0.95–2.57; P = 0.07). In separate models, TP53 mutations showed a strong, independent negative prognostic effect (HR = 2.65; 95% CI, 1.47–4.81; P = 0.001). No other gene mutations showed an independent effect on overall survival in this model.

Similarly, in multivariate analysis of the MI-dnAML subgroup, the presence of ≥3 SNP-A lesions had an independent negative effect on overall survival (HR = 1.92; 95% CI, 1.01–3.68; P = 0.04), as did the presence of ≥4 lesions (HR = 2.50; 95% CI, 1.29–4.84; P < 0.01). In separate models, TP53 mutations likewise showed a strong, independent negative impact on prognosis (HR 4.08; 95%
HR of 1.60 (95% CI, 0.77–3.31) for ≥3 and ≥4 SNP-A lesions, respectively, that were NS (P = 0.02 and 0.19); however, conclusions are limited by the small number of cases (N = 11) that both had an aCNA/cnLOH count ≥3 and were TP53 wild-type.

Multivariate analyses were also performed on the TCGA dnAML group. In models that included age and cytogenetics, DNMT3A and FLT3-ITD mutations showed an independent adverse prognostic effect (HR 1.67; 95% CI, 1.12–2.48; P = 0.01; and HR 1.60; 95% CI, 1.00–2.55; P = 0.04, respectively) with a trend toward an independent adverse effect of TP53 mutations (HR 1.81; 95% CI, 0.92–3.56; P = 0.08; Supplementary Table S5). An independent adverse effect of aCNA/cnLOH count ≥3 in TP53 wild-type or mutant cases was not detected. Analysis of the clinical features of the TP53-mutant and wild-type subgroups within the TCGA and MI-AML groups shows that while the TP53-mutant groups are well matched (median age 67 vs. 68 and BMT as consolidation in 27% vs. 25%, respectively), the TCGA TP53 wild-type subgroup with aCNA/cnLOH count ≥3 harbored substantial differences compared with MI-AML (median age 60 vs. 69 and BMT as consolidation in 67% vs. 18% [P = 0.03]), which may explain the lack of observed effect of elevated genomic complexity on outcomes in the TCGA TP53 wild-type subgroup.

Discussion

Recent publications in AML have underscored the importance of simultaneous analysis of competing genomic variables when determining an individual mutated gene’s association with survival (35–37, 50). While these studies have focused on the relative influence of a given mutant gene compared with a pool of other mutant genes, our study integrates the majority of known recurrently mutated genes with SNP-A-based genomic complexity. We characterized the DNA of leukemic blasts from 156 consecutive patients without AML, induction chemotherapy even in the absence of a co-occurring genomic instability? Are recurrent AML-associated gene mutations other than TP53 more associated with AML initiation or clonal outgrowth rather than with chemotherapy resistance? If so, are the observed relationships of these mutations with AML prognosis in part indirect and due to co-occurrence or conversely the lack of association with either TP53 mutations or genomic instability?

In summary, our data demonstrate that RUNX1 mutations, ASXL1 mutations, SNP 6.0 array-based deletions/cnLOH of 5q, 7q, 12p, and 16q and elevated SNP 6.0 array-based genomic complexity significantly predict partial or complete resistance to induction chemotherapy even in the absence of a co-occurring TP53 mutation. Furthermore, highly adverse prognostic information in AML can be derived from determinations of patient’s age,
karyotype, TP53 mutation status, and/or SNP 6.0 array-based genomic complexity, which should be measured routinely for all patients with AML at diagnosis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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