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Epidemiology of adult acute myeloid leukemia: Impact of exposures on clinical phenotypes and outcomes after therapy

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ABSTRACT

Background: An increased risk of adult myeloid leukemia (AML) has recently been associated with lifestyle and environmental exposures, including obesity, smoking, some over the counter medications, and rural/farm habitats in case control studies. The association of these exposures with AML cytogenetic categories, outcomes after therapy, and overall survival is unknown.
Methods: Relevant exposures were evaluated in a cohort of 295 consecutive AML patients diagnosed and treated at Mayo Clinic in Florida and Arizona. Standard cytogenetic risk categories were applied and reviewed in a central cytogenetic laboratory. The association of epidemiologic exposures with cytogenetic risk, complete remission after therapy, and overall survival was evaluated using logistic and Cox regression models.
Results: A significant association between obesity and intermediate-abnormal cytogenetics was identified (OR: 1.94, $P = 0.025$). Similarly, those with secondary AML were more likely to have poor risk (OR: 2.55, $P < 0.001$) and less likely to have intermediate normal (OR: 0.48, $P = 0.003$) cytogenetics. In multivariate analysis, overall survival was improved for patients ≥60 years receiving intensive (RR: 0.21, $P < 0.001$) and non-intensive therapy (RR: 0.40, $P < 0.001$ compared to no treatment, and was lower for users of tobacco (RR 1.39, $P = 0.032$), and those with poor risk cytogenetics (RR: 3.96, $P = 0.002$) or poor performance status (RR: 1.69, $P < 0.001$). Furthermore, an association between statin use at the time of diagnosis (OR: 2.89, $P = 0.016$) and increased complete remission after intensive chemotherapy was identified, while prior solid organ transplantation was associated with significantly lower complete remission rate after therapy (OR: 0.10, $P = 0.035$).
Conclusion: Our results provide evidence that specific epidemiologic exposures, including obesity, are significantly associated with unique AML cytogenetic risk categories and response to therapy. This supports a link between patient lifestyles, clinical exposures, and leukemogenesis.

1. Introduction

Adult myeloid leukemia (AML) is the most common adult acute leukemia, but its etiology is poorly understood [1]. The mixed-lineage leukemia gene at chromosome 11q23 in topoisomerase II therapy-related AML (tAML) and monosomy 5, del(5q), monosomy 7, and del(7q) in alkylating agent tAML, represent distinct chromosomal abnormalities associated with adverse clinical outcomes [2]. AML in children with Down syndrome is associated GATA1 mutations with excellent outcomes after therapy, but as adults their AML outcomes are similar to average age-matched

Abbreviations: AML, adult myeloid leukemia; CI, confidence interval; CR, complete remission; hAML, AML arising from a prior hematologic malignancy; HCTCI, hematopoietic cell transplantation-specific comorbidity index; MDS, myelodysplastic syndrome; OR, odds ratio; OS, overall survival; RR, relative risk; sAML, secondary AML; SOT, solid organ transplantation; tAML, therapy related AML.

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populations [3]. Important lifestyle and environmental exposures are associated with an increased risk of AML as recognized in prior case-control studies, including obesity, smoking, acetaminophen, and rural/farm habitats, but the impact of these exposures on the clinical phenotype and genotype of AML remains unknown [4–9]. An important question arises regarding the impact of these potentially etiologic exposures on disease phenotype and clinical outcomes, including overall survival after therapy. This may have particular clinical significance as some factors may be modifiable and may influence clinical decisions. We hypothesize that specific exposures may be independently associated with unique cytogenetic abnormalities at AML diagnosis. Therefore, in this exploratory study, we evaluated relevant exposures in a cohort of adult AML patients with confirmed central cytogenetics analysis and examined associations with cytogenetic categories of AML, complete remission (CR) after treatment, and overall survival (OS).

2. Patients and methods

295 AML patients diagnosed and treated at Mayo Clinic Florida or Arizona between July 1995 and October 2012 with cytogenetic data available were included in this retrospective study. Patients with acute promyelocytic leukemia (APL) or chronic myeloid leukemia in blast crisis were excluded. The WHO classification of obesity as BMI $\geq$30 kg/m^2 was applied. The hematopoietic cell transplantation-specific comorbidity index (HCTCI) and Eastern Cooperative Oncology Group (ECOG) performance score were defined as previously reported [10,11]. Toxins were defined as benzene, Agent Orange, petroleum, or ionizing radiation. Regular use of acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), statins, metformin, insulin, or immune suppression therapy was defined by prescription or use of over-the-counter medications at least three times weekly. Immune suppression therapy included current or past use of steroids (dexamethasone or prednisone $\geq$5 mg daily), methotrexate, interferon, azathioprine, tacrolimus, mycophenolate mofetil, or cyclosporine.

Secondary AML (sAML) was defined as AML arising from a prior hematologic malignancy (hAML); de novo myelodysplastic syndrome (MDS) or myeloproliferative neoplasm; or tAML after chemotherapy or radiation therapy [12]. Cytogenetic risk categories were identified as good risk [inv(16), t(16;16), t(8;21)], intermediate-normal, intermediate-abnormal [trisomy 8, t(9;11), other non-defined], or poor risk [$\geq$3 chromosomal abnormalities, monosomal karyotype, −5, 5q−, −7, 7q−, 11q23 (non t(9;11), inv(3), t(3;3), t(6;9), t(9;22))] as described by the National Comprehensive Cancer Network guidelines [12,13]. Therapy for AML was considered intensive by intent to induce complete disease remission including clinical trial enrollment [14–16]. Non-intensive therapy included hypomethylating agents azacytidine or decitabine, low dose cytarabine, and hydroxyurea [17–19]. Date of diagnosis is the date of diagnostic bone marrow biopsy. Date of last follow-up and date of death were identified and confirmed by the Social Security Death Index. Upon review of our data collection, there was a significant amount of missing data for FLT3 ITD mutation (N = 203) and NPM1 mutation (N = 233), and therefore, the risk categories used in our study are defined by cytogenetics alone and molecular mutations were not included in any association analysis. Illicit drug use and specific types of toxins were excluded from any association analysis due to low frequencies of these risk factors.

The primary aim of our study was to evaluate the association of patient characteristics and potentially etiologic exposures with cytogenetic risk categories of AML (poor risk, intermediate-abnormal risk, intermediate-normal risk, good risk). Secondary aims were to evaluate associations of patient characteristics and exposures with CR following intensive chemotherapy and OS.

3. Calculation

In evaluation of our primary aim, we first compared patient characteristics and exposures across the four cytogenetic risk categories of AML using Fisher's exact test in single variable analysis. Subsequently, we examined associations of patient characteristics and exposures with cytogenetic risk categories of AML using odds ratios (OR) and 95% confidence intervals (CI) from multivariable logistic regression models. To evaluate whether any patient characteristics or exposures predict specific cytogenetic risk categories, we created a separate dichotomous category for presence of each cytogenetic risk category (poor risk vs. other, intermediate-abnormal risk vs. other, and intermediate-normal risk vs. other), and assessed associations with each of these four separate dichotomous outcomes using logistic regression models. Multivariable models were adjusted for variables that differed between the four cytogenetic risk groups with a P-value of 0.05 or lower in Fisher exact test analysis. We did not consider good risk cytogenetics as a separate outcome in logistic regression analysis due to the low number of patients in this risk group [20].

The Kaplan–Meier method was used to estimate patient survival following AML diagnosis, censoring at the date of last follow-up. Separately for patients <60 years at diagnosis and those $\geq$60 years at diagnosis, associations of patient characteristics and exposures with survival after AML diagnosis were evaluated using relative risks (RR) and 95% CI from single variable Cox proportional hazards regression models; only risk factors that occurred in more than 5 patients in the given age at diagnosis group were evaluated for association with survival after AML diagnosis. In the subgroup of patients who received intensive chemotherapy, associations of patient characteristics and exposures with CR following intensive chemotherapy were evaluated using OR and 95% CI from single variable and multivariable logistic regression models, where factors associated with CR with a P-value of 0.05 or lower were adjusted for in the multivariable model. No adjustment for multiple testing was made in these exploratory analyses, and P-values of 0.05 or lower were considered as statistically significant. It should be noted that this lack of adjustment for multiple testing increases the likelihood of obtaining a type I error (i.e., false-positive finding), and therefore, our results require validation. All statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

4. Results

Patient characteristics are summarized in Table 1. In evaluation of the primary aim, associations of patient characteristics and exposures with cytogenetics are displayed in Table 2 in single variable analysis. Of the 295 patients, 269 (91.2%) had at least one of the potential exposures identified, and 26 (8.8%) did not have any selected exposures. Without adjusting for any potentially confounding variables, sAML, hAML, and prior MDS, all appeared to be significantly associated with poor risk cytogenetics, while tAML and prior chemotherapy were observed least frequently in the intermediate-normal risk group and most frequently in the small good risk group. All five of these variables (sAML, hAML, prior MDS, tAML, prior chemotherapy) were highly correlated with one another. There were no other significant associations with cytogenetics in single variable analysis.

Results of multivariable analysis assessing associations between patient characteristics and exposures with cytogenetic risk categories of AML are displayed in Table 3. We adjusted our multivariable models for sAML, prior MDS, and prior chemotherapy. We did not additionally adjust for hAML or tAML since these

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