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Research paper

Independent Prognostic Significance of Monosomy 17 and Impact of Karyotype Complexity in Monosomal Karyotype/Complex Karyotype Acute Myeloid Leukemia: Results from Four ECOG-ACRIN Prospective Therapeutic Trials

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ABSTRACT

The presence of a monosomal karyotype (MK+) and/or a complex karyotype (CK+) identifies subcategories of AML with poor prognosis. The prognostic significance of the most common monosomies (monosomy 5, monosomy 7, and monosomy 17) within MK+/CK+ AML is not well defined. We analyzed data from 1,592 AML patients age 17–93 years enrolled on ECOG-ACRIN therapeutic trials. The majority of MK+ patients (182/195; 93%) were MK+/CK+ with 87% (158/182) having ≥5 clonal abnormalities (CK≥ 5). MK+ patients with karyotype complexity ≤4 had a median overall survival (OS) of 0.4y compared to 1.0y for MK- with complexity ≤4 ($p < 0.001$), whereas no OS difference was seen in MK+ vs. MK- patients with CK≥ 5 ($p = 0.82$). Monosomy 5 (93%; 50/54) typically occurred within a highly complex karyotype and had no impact on OS (0.4y; $p = 0.95$). Monosomy 7 demonstrated no impact on OS in patients with CK≥ 5 ($p = 0.39$) or CK ≤ 4 ($p = 0.44$). Monosomy 17 appeared in 43% (68/158) of CK≥ 5 patients and demonstrated statistically significant worse OS (0.4y) compared to CK≥ 5 patients without monosomy 17 (0.5y; $p = 0.012$). Our data suggest that the prognostic impact of MK+ is limited to those with less complex karyotypes and that monosomy 17 may independently predict for worse survival in patients with AML.

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1. Introduction

Despite the increasing use of molecular characterization of mutations in the prognostic risk classification of acute myeloid leukemia (AML), conventional cytogenetic studies at diagnosis remain a highly influential risk factor. The presence of a complex karyotype (CK+) [1,2] or monosomy of either chromosome 5 [3] or chromosome 7 [4] has been universally associated with unfavorable prognosis. Recently the UK MRC added monosomy 17 to its list of independent predictors of poor outcome with their refinement of the AML cytogenetic classification categories [5]. Although there has been no change in induction therapy for nearly 4 decades [6], subgroups that respond particularly well or poorly have been identified based on their genetic features [1,4,5,7–9]. Careful examination of disease characteristics at diagnosis is imperative to identify high-risk patients and to appropriately apply risk-adapted molecularly targeted therapies or intensified treatment strategies including hematopoietic stem cell transplantation (HSCT).

The Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research (HOVON/SAKK) group was the first to demonstrate the potential of monosomal karyotypes (MK) to delineate a subgroup with very poor risk and thus refined the cytogenetic classification of AML patients < 60 years. [8] MK+ was defined as either the presence of two or more autosomal monosomies or one monosomy plus at least one structural abnormality and was associated with a 4% 4-year overall survival (OS) compared to 26% for MK- patients. Particularly unfavorable outcomes in MK + patients > 60 years were reported by the Southwest Oncology Group (SWOG) with a 4-year OS of 1% and less than one third of MK+ patients between ages 31 to 60 years achieved complete remission (CR). [10]

Haferlach and colleagues in the Munich Leukemia Laboratory Group reported that complex karyotype defined as ≥4 unrelated abnormalities identified the largest proportion of very poor risk AML patients and suggested that the combination of CK ≥ 4 and MK+ status would be the most sensitive metric in identifying those with unfavorable prognosis. [11] Additionally, degree of cytogenetic complexity has been shown to identify the subgroups of MDS patients with the worst prognosis, independent of MK+ status. [12,13] In fact, when accounting for karyotype complexity MK was not an independent prognostic factor in patients with myelodysplastic syndrome. [12,13]

Whether the prognostic value of specific monosomies such as monosomy 5, monosomy 7, or monosomy 17 is preserved in the context of MK+ AML is uncertain. Therefore, we conducted a retrospective analysis of AML patients enrolled in four Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network Cancer Research Group (ECOG-ACRIN) therapeutic clinical trials between 1990 and 2008 to determine whether individual monosomies, karyotype complexity, age, or baseline disease characteristics impact outcome in MK+ disease.

2. Methods

2.1. Patients

Eligible patients for this study were defined as previously untreated AML patients enrolled in one of four prospective ECOG-ACRIN therapeutic clinical trials (E1490, E1900, E3993, and E3999) between 1990 and 2008. [14–17]

Newly diagnosed AML patients (excluding acute promyelocytic leukemia) were eligible for enrollment onto the therapeutic protocols. Except for those enrolled onto E1900, patients were required to be at least 55 years of age. All patients received induction chemotherapy containing cytarabine combined with daunorubicin, idarubicin, or mitoxantrone ± additional investigational agents as defined by the respective protocol. Post-remission therapeutic strategies were defined per individual protocol and not influenced by the identification of MK+ disease. All patients signed informed consent prior to enrollment. The studies were approved by ethics committees of all participating institutions and conducted in accordance with the Declaration of Helsinki. A total of 1,592 AML patients ranging 17–93 years of age were enrolled on the aforementioned trials.

Evaluable cytogenetics data are available on 1,188 patients included in this analysis. Patients enrolled on E1900 accounted for the largest number of the 1,188 patients (45%; 535), followed by those on E3999 (29%; 345), E3993 (22%; 266), and E1490 (4%; 42).

2.2. Cytogenetic evaluation

Diagnostic bone marrow aspirate or heparinized peripheral blood was examined for cytogenetic abnormalities by unstimulated standard culturing and banding techniques by individual institutional or referral cytogenetic laboratories. Results and karyotypes were centrally reviewed by the ECOG-ACRIN Cytogenetics Committee and designated in accordance with the International System for Human Cytogenetic Nomenclature (ISCN). Karyotypic analysis was based on minimum review of 10 available metaphases. Normal karyotype required a minimum of 20 normal diploid metaphases. Abnormalities were considered clonal when at least 2 metaphases had the same structural abnormality or the same trisomy or when at least 3 metaphases displayed the same monosomy. Structural abnormalities were defined as deletions, translocations, inversions, and additions for the purposes of this study and in accordance with the definition used by HOVON/SAKK [8]. The following clonal abnormalities were scored for each chromosome: monosomies, extra copies, structural abnormalities, ring chromosomes as well as the frequency of the individual abnormalities. Marker chromosomes and double minutes were also documented. Complex karyotype was defined as ≥ 3 clonal abnormalities in accordance with the National Comprehensive Cancer Network [18] and the European Leukemia Net recommendations [19]. Degree of cytogenetic complexity was also recorded for CK+ patients having 3, 4, or ≥5 clonal abnormalities. Patients with core-binding factor (CBF) leukemia [t(8;21), inv(16) or t(16;16)] were excluded from the MK+ cohorts regardless of the presence of additional clonal abnormalities.

2.3. Statistical Analysis

Patient baseline characteristics were compared using Fisher's exact test if they were categorical and Wilcoxon rank sum tests if they were continuous. OS was defined as time from study randomization/registration to death from any cause, with follow-up censored at the date of last contact. Kaplan-Meier estimates were used to estimate the event-time distributions for OS. Log-rank tests stratified on studies and induction treatments were used to examine the effects of MK or other chromosomal abnormalities on OS. Multivariate Cox model stratified on studies and induction treatments was performed on OS to examine the prognostic effect of MK or other chromosomal abnormalities while controlling for potential risk factors {Multivariate analysis included the factors of MK+ status, karyotype complexity, gender, age, WBC count, hemoglobin, platelet count, marrow and blood blast %, secondary vs de novo AML, and the occurrence of independent high-risk cytogenetic abnormalities [del5q, del7q, del17p, inv3, t(6;9), 11q23, and t(9;22)] where appropriate}. All P values were based on 2-sided tests.

3. Results

3.1. Cytogenetic Abnormalities

Cytogenetics were evaluable in 1188/1592 (75%) of AML patients enrolled onto the four protocols. An overview of the frequency of normal as well as clonal cytogenetic abnormalities is seen in Table 1. Normal karyotype AML occurred in 502 (42%) patients whereas 686 (58%) had clonal cytogenetic abnormalities. CBF leukemia was identi-