OPEN

Citation: Blood Cancer Journal (2013) 3, e122; doi:10.1038/bcj.2013.21

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LETTER TO THE EDITOR

Monosomal karyotype in Philadelphia chromosome-negative acute lymphoblastic leukemia

Blood Cancer Journal (2013) **3,** e122; doi:10.1038/bcj.2013.21; published online 5 July 2013

A monosomal karyotype (MK) is defined by the presence of two or more autosomal monosomies or one autosomal monosomy and one or more structural abnormality.[1] MK has been shown to have a negative impact on survival in patients with acute myeloid leukemia,[1–6] primary myelofibrosis[7] and myelodysplastic syndromes.[8] In several studies, the negative prognostic significance of MK in myeloid neoplasms persisted after treatment with allogeneic stem cell transplantation.[9,10] A recent analysis from Spain failed to demonstrate an independent prognostic significance of MK in myelodysplastic syndromes.[11]

Multiple recurring chromosomal alterations have been identified in acute lymphoblastic leukemia (ALL). The World Health Organization 2008 classification recognizes the following recurring genetic abnormalities: t(9;22)(q34;q11.2);BCR-ABL, t(v;11q23); MLL rearrangement, t(12;21)(p13;q22); TEL-AML1(ETV6-RUNX1), hyperdiploidy, hypodiploidy, t(5;14)(q31;q32) IL3-IGH and t(1;19)(q23;p13.3);TCF3-PBX1.[12] Several cytogenetic risk classifications in adult ALL were introduced during the last decade.[13–15] Although there are subtle differences between these, the overall assignment to favorable or unfavorable risk categories is concordant. Most analyses demonstrated a negative prognostic value for karyotypes with hypodiploidy, t(9;22), t(4;11), t(8;14), MLL translocations and for complex karyotypes (defined as the presence of five or more chromosomal abnormalities, excluding those with established translocations). In a large cytogenetic analysis of 1522 adult patients treated in the Medical Research Council UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial, four prognostic karyotype categories were identified: standard risk ALL (hyperdiploid karyotype), intermediate risk ALL (11q abnormalities (other than MLL), del(17p), del(6q), del(9p), del(12p), -13, t(14q32), t(10;14), low hyperdiploidy (47–50 chromosomes), tetraploidy, normal and all others), high-risk ALL (-7, $+8$, MLL rearrangements, t(1;19), t(17;19), t(5;14)) and very-high-risk ALL (t(4;11), t(8;14), complex karyotype ($\geqslant$ 5 abnormalities), low hypodiploidy and near triploidy).[14]

MK in ALL has not been evaluated thus far. The goal of this study was to evaluate the incidence, clinical characteristics and prognosis of a MK in Philadelphia chromosome-negative ALL (Ph Neg ALL).

This study was approved by the Mayo Clinic Institutional Review Board. The Mayo Clinic leukemia database was used to identify consecutive patients with newly diagnosed ALL. Patients were stratified by cytogenetic risk categories using the four-karyotype risk model proposed by the MCR UKALLXII/ECOG 2993 analysis.[14] All cytogenetic results were reviewed to identify patients with a MK. Outcomes analyzed included overall survival (OS) calculated from the date of diagnosis, leukemia-free survival (LFS) and relapse rates. Chi-square test was used to compare the variables. Survival was estimated and compared by using the Kaplan–Meier Method and the log-rank test, respectively. Multivariate analysis was performed using the Cox regression model.

Between 1998 and 2010, a total of 175 consecutive patients with ALL (63 (36%) with the Philadelphia chromosome) were identified. Patients with Ph+ ALL were excluded from further analysis.

In the study set of patients with Ph Neg ALL (112 patients), the median age was 39 years (16–88). Seventy-four (66%) were male patients. Cytogenetic risk stratification revealed standard risk cytogenetics in 5 (4.4%), intermediate risk in 70 (62.5%), high risk in 8 (7.1%) and very-high risk in 29 (25.9%) patients. Twenty-two patients (20.9%) presented with extramedullary disease (13 patients with central nervous system disease; 12%). Six had prior exposure to chemotherapy. Complete blood counts at presentation were as follows: median hemoglobin 10 g/dl (4.1–18.5), median platelet count 61×10^9/l (3–523) and median white blood cell count 7.2×10^9/l(0.8–377). Thirty-four (39.3%) patients underwent allogeneic stem cell transplantation.

The median OS for the whole cohort was 41 months (0–206). The median LFS was 29 months (0–193). Ninety-one patients (81.3%) achieved an initial complete response and 44 (39.3%) had a subsequent relapse after achieving an initial complete remission, with a median time to relapse of 15 (2–73) months.

Out of these 112 patients with Ph Neg ALL, MK was identified in 19 patients (16.9%). The median age at presentation in these 19 patients was 39 (16–81) years. Twelve patients (63.2%) were male

Table 1. Baseline clinical and laboratory characteristics of 112 patients with Philadelphia chromosome-negative acute lymphoblastic leukemia stratified by the presence or absence of a monosomal karyotype

Variable	*MK (19 patients)*	*No MK (93 patients)*	P-*value*
Median age (range)	39 (16–81)	40 (18–88)	0.8
Gender (male)	12 (63.2%)	62 (66.7%)	0.8
Median hemoglobin at diagnosis, g/dl (range)	9.5 (5.4–14.0)	10 (4.1–18.5)	0.7
Median WBC count at diagnosis, $\times 10^9$/l (range)	8.3 (0.8–300)	7.0 (1.2–377)	0.9
Median platelet count at diagnosis, $\times 10^9$/l (range)	34 (8–523)	61 (3–499)	0.6
Cytogenetic categories			
High or very high	16 (84%)	21 (23%)	0.0001
Standard or intermediate	3 (16%)	72 (77%)	
Extramedullary disease	3 (16%)	19 (20%)	0.7

Abbreviations: WBC, white blood cell; MK, monosomal karyotype.

and three (16%) presented with extramedullary disease. The MK in these 19 patients included two or more autosomal monosomies in 3 (16%, all had hypodiploid karyotype) and one autosomal monosomy plus one or more structural abnormalities in 16 (84.2%) patients. The median hemoglobin at presentation was 9.5 g/dl (5.4–14.0), the median white blood cell count was 8.3×10^9/l (0.8–300) and the median platelet count was 34×10^9/l (8–523). In 16 of these 19 patients with MK (84.2%), cytogenetic risk categories were high or very high regardless of the MK status (4 patients (21.1%) with high risk and 12 patients (63.2%) with very-high-risk cytogenetics). All of these patients received intensive chemotherapy, and 6 (31.5%) were treated with allogeneic stem cell transplantation. Table 1 compared the characteristics of patients with Ph Neg ALL, stratified by the presence or absence of a MK.

The OS in patients with Ph Neg ALL was inferior when MK was present. However, this difference did not meet the statistical significance. The median OS was 24 months when MK was present compared with 50 months when MK was absent, $P = 0.5$, Figure 1. Similarly, the 3-year survival rates and LFS were inferior when MK was present (3-year survival rates of 31.6% vs 53%, $P = 0.5$ and LFS of 13 vs 32 months, $P = 0.2$). In addition to that the OS in patients with MK was similar to that in patients with high or very-high-risk cytogenetics with no MK (24 vs 20 months, respectively, $P = 0.3$).

A multivariate analysis identified platelet count at diagnosis ($P = 0.045$, hazard ratio (HR) 0.5, 95% confidence interval (CI) = 0.2–0.8), cytogenetic risk categories ($P = 0.006$, HR 0.6, 95% CI = 0.1–0.9) and ECOG performance status ($P = 0.0004$, HR 3.1, 95% CI = 1.6–4.3) as independent prognostic factors for OS. Variables included in this model were: sex, complete blood count at diagnosis, MK, lactate dehydrogenase, extramedullary presentation, performance status and cytogenetic risk categories.

Our study shows that MK in Ph Neg ALL is closely related to high-risk cytogenetics and is not an independent prognostic factor. The incidence of MK in Ph Neg ALL in our cohort was 17%. The majority of these patients (86%) had high or very-high cytogenetic risk categories and 63% met the criteria for a complex karyotype, regardless of their MK status.

The close association of MK with high-risk cytogenetics has also been demonstrated in previous analyses of MK in myeloid diseases. In 184 AML patients with MK, Breems *et al.*[1] found that 81% of these patients also met the criteria for complex karyotype and 80.4% had at least one established unfavorable cytogenetic abnormality. An analysis of 127 myelodysplastic syndrome patients with MK demonstrated an association with high-risk features (intermediate two or more categories on the international prognostic scoring system) in 97% of cases.[8]

In conclusion, the current analysis suggests that MK is relatively uncommon in Ph Neg ALL and unlike in myeloid neoplasms, is not an independent prognostic factor affecting OS.

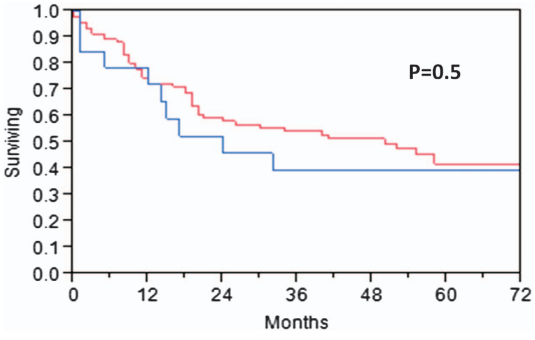

Figure 1. Kaplan–Meier survival curves for 112 patients with Philadelphia chromosome-negative acute lymphoblastic leukemia stratified by the presence (blue curve, median survival 24 months) or absence of monosomal karyotype (red curve, median survival 50 months).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SS Kenderian, A Al-Kali, N Gangat, L Letendre, WJ Hogan, MR Litzow and MM Patnaik
Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
E-mail: Patnaik.mrinal@mayo.edu

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