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ORIGINAL ARTICLE

Determining the frequency of iron overload at diagnosis in de novo acute myeloid leukemia patients with multilineage dysplasia or myelodysplasia-related changes: a case control study

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Abstract

Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) is a new disease category, which was defined as a separate entity in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. While pre-treatment iron overload in patients with myelodysplastic syndrome has been previously studied, its relationship with AML-MRC has not been studied. We aimed to investigate the relationship between serum iron tests compatible with iron overload and the diagnosis of multilineage dysplasia (MLD) and AML with myelodysplasia-related changes (AML-MRC) in AML patients diagnosed at Hacettepe University Adult Hospital between January 2002 and September 2017. Ninety-three patients who met the criteria were enrolled. Bone marrow aspirate of each patient was re-examined, and dysplasia was investigated; other data were examined from patient's records. The iron overload status at diagnosis and transferrin saturation (TS) values were compared between the groups with and without MLD and those with and without AML-MRC. When iron overload was defined as TS ≥ 58% and ferritin ≥ 500 ng/mL, iron overload was observed in 10 (37%) patients with MLD and in 4 (13%) without MLD. The difference is almost statistically significant ($p = 0.053$). The mean TS value and frequency of iron overload were higher in AML-MRC patients than in non-AML-MRC patients ($p < 0.05$ for both). A mild positive significant correlation was observed between the dysplasia severity score and TS ($r = 0.317$, $p = 0.032$). In patients with AML-MLD and AML-MRC, iron overload occurred regardless of the transfusion status at the time of diagnosis. Morphologic severity of dysplasia may be correlated with higher TS values at the time of diagnosis.

Keywords Acute myeloid leukemia · AML with myelodysplasia-related changes · Iron overload · Multilineage dysplasia · Transferrin saturation

Introduction

Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) is a relatively new disease category, which was defined as a separate entity in the 2008 World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues [1] and has remained in the 2016 revision [2]. Before the addition of myelodysplastic syndrome (MDS)-related cytogenetic abnormalities to the criteria, the entity was referred to as AML with multilineage dysplasia (AML-MLD), which was defined in 1987 by Brito-Babapulle et al. [3].

Iron overload frequently occurs in newly diagnosed MDS patients [4, 5]. This phenomenon has not been studied in patients with AML-MRC or in cases with AML-MLD.

In this study, we investigated whether AML-MLD or AML-MRC patients, which are entities sharing many similarities with MDS, including both morphological dysplasia and similar cytogenetic abnormalities [1, 6] as well as similar mitochondrial gene transcription anomalies [7], are prone to iron overload at diagnosis and whether dysplasia severity is

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correlated with iron overload. We also aimed to investigate whether iron overload has a predictive value in the diagnosis of AML-MRC, which can be difficult to diagnose based only on the morphological criteria.

Materials and methods

Patients and study plan

The data of patients diagnosed with AML between December 2001 and April 2017 at Hacettepe University Faculty of Medicine, Department of Hematology were analyzed.

Patients aged over 18 years whose serum iron tests were sent at the time of diagnosis were enrolled in the study.

By contrast, patients who were previously diagnosed with MDS or MDS/MPN or with known anemia (or other cytopenias) > 1 month before diagnosis, with known liver disease or nephrotic syndrome, who received iron supplements in the last 3 months, who did not undergo bone marrow aspiration based on the archival records of the Department of Pathology of the Faculty of Medicine of Hacettepe University were excluded.

Patients were classified as AML-MRC and non-AML-MRC based on the 2016 revision WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [2] as described below.

Histomorphological examinations and the diagnoses of AML-MLD and AML-MRC

May-Grünwald-Giemsa-stained marrow smears of each patient were examined to detect the presence of histomorphological dysplasia. Prussian blue-stained smears were also evaluated for presence of pathological sideroblasts.

AML-MRC-compatible dysplasia in a specific major myeloid hematopoietic line was defined as at least 50% dysplastic precursors in the marrow. Dysplastic morphological criteria were as follows: nuclear alterations (budding, internuclear bridging, karyorrhexis, and multinuclearity), cytoplasmic features (megaloblastoid changes, vacuolization, cytoplasmic blebs), or at least 15% ring sideroblasts for dyserythropoiesis, hypogranular cytoplasm, hypo-segmented nuclei, or bizarrely segmented nuclei for dysgranulopoiesis, micromegakaryocytes, and normal-sized or large megakaryocytes with non-lobated or multiple nuclei for dysmegakaryopoiesis as defined by the WHO. Dysplasia must be present in at least two myeloid cell lines (i.e., multilineage dysplasia) in order to diagnose a patient with marrow dysplasia, which is compatible with AML-MRC. Ten precursor cells of each hematopoietic line had to be counted for this line to be considered eligible for evaluation of dysplasia. Microscopic examinations were performed by an experienced hematologist (YB). Thirteen patients with borderline (40–60%) dysplasia in at least one line were re-evaluated, and their status was confirmed by an experienced hematopathologist (AÜ).

Patients with AML-MLD (if not otherwise classified depending on cytogenetic data) and those who had compatible cytogenetic abnormalities constituted the AML-MRC group.

Dysplasia severity score

Using the dysplasia severity score, each line that had at least 50% dysplasia was scored between 1 and 5. This scoring aimed to grade objective dysplasia and was developed for the purpose of this study. The frequency of dysplastic features that are considered most objective for each line was taken into consideration when assigning this score. These features included multinuclearity and nuclear budding for the erythroid line, pelgeroid forms for the myeloid line, and micromegakaryocytes for the megakaryocytic line. The lines with < 50% dysplasia were scored with 0. If a hematopoietic line had ≥ 50% dysplasia and a < 10% ratio of precursor cells with objective dysplastic findings, the dysplasia severity score was 1. An increasing score was assigned when objective dysplasia was higher with the score 5 corresponding to objective dysplasia rate of ≥ 40% in the analyzed hematopoietic line. The total dysplasia severity score was the sum of each three lines' scores for each patient.

Cytogenetic studies

Cytogenetic studies were carried out by Ankara University Medical Faculty Medical Genetics Department Laboratory for patients diagnosed before 2009 and by Cytogenetics Laboratory of Department of Basic Oncology of Hacettepe University for patients who were diagnosed in or after 2009. The technique involved culturing the marrow specimen for 24 h then karyotyping with Giemsa banding (GTG). The cytogenetic risk stratification was performed according to the European Leukemia Network (ELN)'s "Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel" [8]. Reporting of at least 20 metaphases was deemed necessary for a cytogenetic analysis to be considered sufficient. Insufficient analyses were excluded.

Serum iron testing

Each patient underwent serum iron tests at the day of diagnosis.

Serum iron tests were performed by the staff from the Clinical Pathology Laboratory of Adult Hospital of Hacettepe University. Serum iron concentration and serum iron binding capacity measurements were made using Roche

Cobas Integra 800 (Roche Diagnositcs, Risch-Rotkreuz, Switzerland) until 2012 and Beckman Coulter AU5800 devices (Beckman Coulter Inc., Brea, CA, USA) post-2012. Acidification with 2,4,6-tripyridyl-striazine (TPTZ) was used for serum iron concentration determination, and serum iron binding capacity was measured using the "indirect method" [9].

Serum ferritin assay was performed using Beckman Coulter DXI 800 Immunoassay System devices (Beckman Coulter Inc., Brea, CA, USA) until 2012 and post-2012 with Abbott Architect devices (Abbott Diagnostics, Lako Forest, IL, USA) using immunoenzymatic sandwich method.

Transferrin saturation (TS) values were obtained by calculating the total iron binding capacity (TIBC) and serum iron using the formula: [serum iron (μmol/L)/total serum iron binding capacity (μmol/L)] × 100.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (IBM Inc., Armonk, NY, USA) software versions 17 and 23. The variables were examined by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) to determine if they were normally distributed or not. Descriptive statistics were presented as mean and standard deviation for normally distributed variables; median, minimum-maximum, and interquartile range (IQR) for non-normally distributed variables; and frequencies for nominal variables. The Mann-Whitney *U* test and independent samples Student's *t* test were used to compare non-normally and normally distributed variables, respectively. Chi-square or Fischer's exact tests were used as appropriate when comparing percentages. The correlation between TS and total dysplasia severity score was assessed using Spearman's test. Statistical significance was considered when the value of p was below 0.05.

Results

Of the 452 de novo AML patients seen during the study period, 93 (about 20%) were included in the study. Thirty-two patients of the initial cohort were excluded because they fulfilled the exclusion criteria (use of oral or IV iron replacement, chronic kidney or hepatic disease, long-term cytopenia before diagnosis, etc.); others were excluded because serum iron tests were not performed at the day of diagnosis.

Patient characteristics

Of the 93 AML patients enrolled, 43 (46%) were female and 50 were male. The median age at diagnosis was 54 (18–82) years. Seven patients had acute promyelocytic leukemia (APL). The patients had received an average of 1 (0–7, IQR 3) unit of red blood cell (RBC) suspension transfusions before the diagnosis.

Patients had mean hemoglobin concentration of 8.9 (± 2.1) mg/dL, median white blood cell count (WBC) of $5.7 \times 10^3/\mu L$ (0.4–291.8), and mean platelet count of $53 \times 10^3/\mu L$ (6–2653) at diagnosis.

Descriptive statistics of patients' serum iron parameters at the time of diagnosis are shown in Table 1.

Cytogenetic analysis was performed in 75 non-APL patients, but sufficient metaphases were not reported in 31 (41%) patients. Cytogenetic abnormalities were observed in 25 patients (33%). Complex aberrant karyotype was observed in 10 patients (13%). About 14 patients (16%, 56% of those with cytogenetic abnormalities) were in poor cytogenetic risk class, while 3 (4%) were in good cytogenetic risk class. MDS-related karyotypes were observed in 17 (20%) patients in this group.

Histomorphological examination results

The dysplasia status of 22 patients (23%) was not determined due to the presence of blastic infiltration in the bone marrow with very few remaining precursor cells. The details of the examinations are shown in Fig. 1.

When the cytogenetic data were also taken into consideration, patients were classified as AML-MRC ($n = 32$) and non-AML-MRC ($n = 14$). Some important characteristics of the patients with or without AML-MRC and those with or without AML-MLD are presented in Table 2.

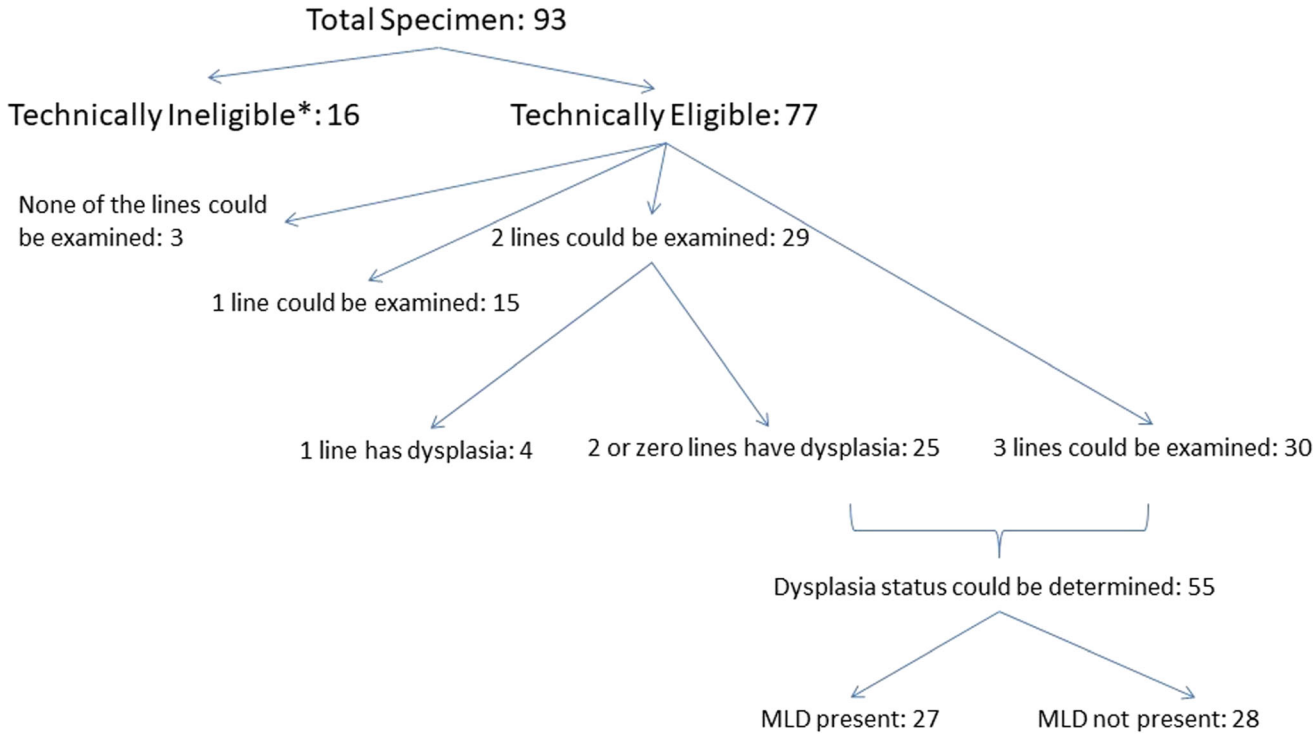
There was no statistically significant difference in mean hemoglobin concentrations, WBC count, or platelet counts between groups (AML-MRC vs. non-AML-MRC and AML-MLD vs. non-AML-MLD) (data not shown).

Comparison of serum iron tests at the time of diagnosis between groups with and without AML-MLD

There was no significant difference in baseline blood cell count and hemoglobin values and amount of RBC transfusions between the MLD group and non-MLD group or AML-MRC and non-AML-MRC group (for both $p > 0.05$, data not shown). The comparison of serum iron tests between

Table 1 Descriptive statistics of serum iron tests at the time of diagnosis

Serum iron (μg/dL)	121.5 ± 61.4
Total iron binding capacity (μg/dL)	234.6 ± 59.6
Ferritin (ng/mL)	554 (5–6126)
Transferrin saturation (%)	53.4 ± 26.1



*Due to absence of marrow particules in the smear or due to the quality of staining

Fig. 1 Patients' distribution according to histomorphological examination

group with or without AML-MRC and those with or without AML-MLD are shown in Table 2.

In summary, all the serum iron markers were higher (and TIBC lower) in patients with dysplasia compatible with AML-MRC, although none of the comparisons were statistically significant. When iron overload was arbitrarily defined as having both ≥ 500 ng/ml ferritin and ≥ 58% TS, its frequency was higher in patients with AML-MLD and the difference was almost statistically significant ($p = 0.053$).

Table 2 Characteristics of patients with or without AML-MRC and those with or without AML-MLD at diagnosis

	AML-MLD ($n = 27$)	Non-AML-MLD ($n = 28$)	AML-MRC ($n = 32$)	Non-AML-MRC ($n = 14$)
Age (IQR*)	54 (14)	47 (33.2)	56.5 (14.2)	42 (29.7)
Gender (M/F**)	14/13	16/12	18/14	8/6
Serum iron (μg/dL) ± SD***	135.8 ± 3.1	117.5 ± 51	136.78 ± 62.5	116.29 ± 47.8
Total iron binding capacity (μg/dL) ± SD	249.3 ± 77.9	261.4 ± 66.4	244.4 ± 73.3	286.3 ± 68.5
Ferritin (ng/mL) (IQR)	517 (629)	425 (614)	538 (697)	295 (576)
Transferrin saturation (%) ± SD	57.6 ± 26.1	47.3 ± 21.8	58.9 ± 26.6	42.4 ± 17.9
Iron overload**** [*n* (%)]	10 (37%)	4 (13%)	13 (40%)	1 (7%)

*Interquartile range

**Male/female

***Standard deviation

****Defined as TS ≥ 58% and ferritin ≥ 500 ng/mL

Overall and disease-free survival analyses were performed in patients with and without iron overload, and the results showed no significant difference (data not shown).

Comparison of serum iron tests at the time of diagnosis between AML-MRC patients and non-AML-MRC patients

Mean serum transferrin saturation at the time of diagnosis was 58.9% (SD ± 26.6) in the AML-MRC group and 42.4% (SD ± 17.9) in the non-AML-MRC group. The difference was statistically significant ($p = 0.019$).

When iron overload was defined as above, iron overload at diagnosis was reported in 13 (40%) AML-MRC patients and in 1 (7.1%) non-AML-MRC patient. The difference was also statistically significant ($p = 0.032$).

Presence of iron overload provided a sensitivity of 40.6% (95% confidence interval [CI] 23.7–59.3%) and a specificity of 92.8 (95% CI 66.1–99.8%) for diagnosing AML-MRC. The positive predictive value was 92.8% (95% CI 65.2–98.9%), and the negative predictive value was 40.6% (95% CI 33.1–48.5%).

A statistically significant moderate positive correlation was observed between total dysplasia severity score and transferrin saturation ($r = 0.317$, $p = 0.032$) (Fig. 2).

Discussion

This study evaluated AML patients who were diagnosed in Hacettepe University School of Medicine, Department of Internal Medicine, Section of Hematology between January 2002 and September 2017, for whom serum iron tests were requested at the time of diagnosis, who met the other study criteria.

Our results revealed that the mean transferrin saturation values of AML-MRC patients at the time of diagnosis were higher than those without AML-MRC (58.9% vs 42.4%, respectively). Moreover, the rates of presentation with iron overload were higher when iron overload was defined as TS ≥ 58% and ferritin ≥ 500 ng/mL. The fact that patients with preceding history of MDS and those who were followed up for more than 1 month due to anemia before they were diagnosed were not included in the study suggests that this situation was not related to RBC transfusions. Besides, the existing data indicated that there was no difference in the number of RBC units transfused between groups. This study primarily aimed to investigate if there was a relationship between AML-MLD/AML-MRC and serum iron tests suggesting iron overload at the time of diagnosis (i.e., before transfusion therapy was initiated). Therefore, it is plausible to select various elevated cut-off levels for ferritin and TS. A

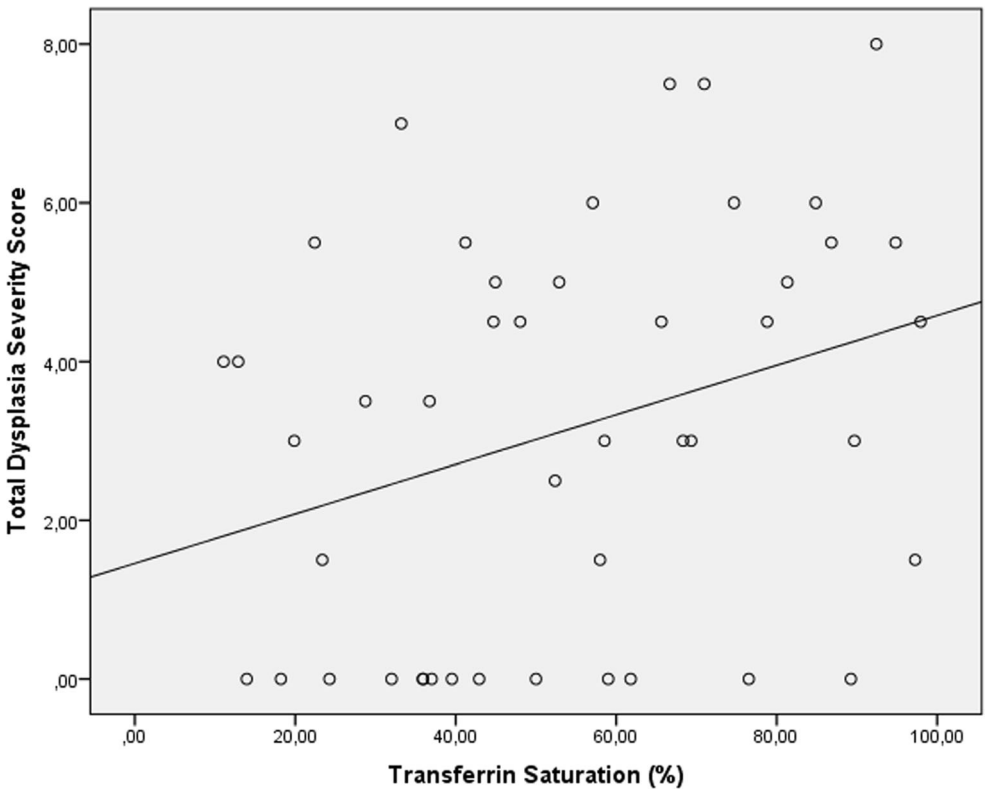


Fig. 2 Correlation between total dysplasia severity score and transferrin saturation in AML-MRC and non-AML-MRC patients

relationship was observed when the cut-off for iron overload was described as TS ≥ 58% and ferritin ≥ 500 ng/mL.

While it has long been observed by the clinicians that MDS patients have iron overload even before transfusion was administered, it is a phenomenon taking part in medical literature since 2000s [4, 5]. A study conducted by Cortelezzi et al. indicated that non-transfused MDS patients had iron overload, the level of non-transferrin bound iron (NTBI) was higher in MDS patients, and low NTBI levels were associated with higher risk for MDS and higher leukemic transformation. Furthermore, they suggested that high iron consumption of blast cells could be the reason [4]. A study conducted by Cui et al. in 2006 suggested that MDS patients who were not transfused yet had iron overload possibly due to the presence of growth differentiation factor 15 (GDF-15) secreted by mature erythroblasts [5]. Increased iron absorption from the intestine due to altered metabolism of hepcidin has also been suggested as a cause [10, 11].

MDS and AML-MRC are two diseases that share similar histomorphological bone marrow dysplasia and cytogenetic abnormality profiles [2]. A study conducted by Schildgen et al. in 2011 revealed that these two diseases had similar mitochondrial DNA expression anomaly profiles [7]. Therefore, it is plausible that iron overload occurs in patients with AML-MRC through similar mechanisms (as in MDS) prior to the initiation of blood transfusion. This phenomenon was not previously investigated in patients with de novo AML or AML-MRC.

When MLD was considered alone, TS was higher in AML patients with MLD than those without MLD (57.6% and 47.3%, respectively) at diagnosis; however, the difference was not statistically significant. Again, iron overload was observed more frequently in patients with MLD than those without MLD at the time of diagnosis (37% and 13%, respectively) and the difference was almost statistically significant. This finding suggests that morphological dysplasia may represent genetic or functional changes underlying iron overload as discussed above.

The positive predictive value of iron overload in terms of AML-MRC was 92.8%, while the negative predictive value was 40.6%. We presume that testing for iron overload via serology during initial evaluation of patients who had a preliminary diagnosis of AML may be useful—although not diagnostic—in recognizing AML-MRC.

One interesting finding was the moderate positive statistically significant correlation between total dysplasia severity score and transferrin saturation reported in this study. This finding suggests that the increased rate of iron overload observed in AML-MRC patients at the time of diagnosis was caused by ineffective hematopoiesis. Previously, Ballen et al. and Weinberg et al. proposed and used similar methods to grade the severity of marrow dysplasia in AML patients [12, 13]. The most objective dysplastic findings were used to evaluate these patients. We followed a similar strategy in order to eliminate subjectivity as much as possible; we selected only unequivocal and relatively frequent dysplasia signs to grade. All of the parameters we selected had been used by said previous authors. However, we preferred not to use some of the parameters used in Ballen et al.'s study: erythroid megaloblastic characteristics, leukocyte granulation abnormalities, etc.

This study had some limitations. As there were several patients without sufficient cytogenetics data, those diagnosed with AML-MRC or non-AML-MRC according to cytogenetic criteria alone were represented at a low level. This limitation strikes as perhaps the most important one given the recent emphasis on genetic and molecular methods in diagnosing AML-MRC [14, 15]. Therefore, we can say that the results of this study demonstrated an association between MLD, its degree, and iron overload in AML. However, further studies are warranted to confirm this relationship and probably to determine the most appropriate technique of implementing serum iron test results in the diagnostic process. Our findings on the assessment of AML-MRC patients should also be confirmed using larger cohorts with adequate cytogenetic data.

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Compliance with ethical standards

This study was approved by the Ethics Committee for Non-Interventional Clinical Investigations of Hacettepe University on December 27, 2017 (decision number GO 17/794-28).

Conflict of interest The authors declare that they have no conflict of interest.

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