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ORIGINAL ARTICLE

Whole-arm translocation of der(5;17)(p10;q10) with concurrent *TP53* mutations in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS): A unique molecular-cytogenetic subgroup

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Der(5;17)(p10;q10) is a recurrent but rare aberration reported in myeloid neoplasms (MNs). We report 48 such patients including 19 acute myeloid leukemia (AML) and 29 myelodysplastic syndrome (MDS), to characterize their clinicopathological features. There were 29 men and 19 women, with a median age of 61 years (range, 18–80). 62.5% patients had therapy-related diseases (t-MNs), 70.8% had multilineage dysplasia and 83.3% showed complex karyotypes. In 39 patients tested, *FLT3*, *NPM1*, *CEBPA*, *KIT* were all wild type and *NRAS, KRAS, IDH1, APC*, *TET2* mutations were detected in single case(s) respectively. *TP53* mutations were identified in 8 of 10 cases (80%) tested. Median disease-free survival (DFS) and overall survival (OS) were 3 and 10 months, respectively and did not differ between AML or MDS cases, or between *de novo* versus therapy-related cases, or between the groups with or without complex karyotypes. In 19 patients who achieved complete remission after chemotherapy, and in 9 patients who underwent stem cell transplantation, the OS was better (14 and 17.5 months, $P = 0.0128$ and $P = 0.0086$, respectively). The der(5;17)(p10;q10) represents a unique molecular-cytogenetic subgroup in t-MNs and, associated with complex karyotypes. *TP53* inactivation, resulting from 17p deletion coupled with *TP53* mutation, likely contributes to the poor clinical outcome of these patients.

Keywords Der(5;17), complex karyotypes, *TP53*, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS)

Introduction

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are genetically heterogeneous categories of myeloid neoplasms (MNs). Recurrent clonal cytogenetic abnormalities occur in ~50% of *de novo* AML (1) and ~45% of *de novo* MDS (2) and these abnormalities have critical implications for patient outcome. Therapy-related MNs (t-MN, or t-AML/t-MDS) are a distinct group recognized specifically in the World Health Organization (WHO) classification that arise in patients who have been treated with cytotoxic therapies, such as alkylating agents or topoisomerase II inhibitors or radiation therapy (3). Recurrent clonal chromosomal aberrations are reported in ~70% of these t-MN cases (4).

Traditional chromosome analysis is a standard diagnostic tool utilized to identify specific cytogenetic subgroups that facilitate the risk stratification of patients with MNs. For examples, core binding factor translocations e.g. t(8;21)/*RUNX1-RUNX1T1* or inv(16)/t(16;16)/*CBFB-MYH11* in AML, and 5q deletions in MDS are considered as low risk cytogenetic

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subgroups. In contrast, chromosome 3q aberrations, a monosomal karyotype i.e. monosomy 7, or complex karyotypes are recognized as high-risk genetic/genomic subgroups. Therapy-related MNs (t-MNs), in part because of their cytogenetic alterations, are also a high-risk group of MNs (3,4).

Complex karyotypes, defined as the presence of three or more chromosomal aberrations often involving both structural and numerical abnormalities (5,6) are frequently observed in both MNs and t-MNs (4,7,8). Commonly, complex karyotypes carry partial or whole chromosome loss of chromosome 5 and/or chromosome 7, known to be associated with poor clinical outcomes in patients with AML or MDS (9,10). Monosomy 7 or 7q deletion is most commonly observed and reported in about half of patients with AML/MDS associated with complex karyotypes. Some of these 7q deletions are the result of whole-arm unbalanced translocations of der(1;7)(q10;p10) or der(7;12)(p10;q10)/dic(7;12) (11–13). However, in general whole-arm translocations are rare in hematological malignancies and usually present as part of a complex karyotype (14). Among these whole arm translocations, der(5;17)(p10;q10) or dic(5;17)(q11.2;p11.2) resulting in deletions of chromosomes 5q and 17p, is a very rare recurrent chromosomal aberration reported in MNs (15). To date, very few patients with MN associated with der(5;17)(p10;q10) have been studied (15–20) and their clinicopathological features are not fully characterized. It is postulated that *TP53*, located at chromosome 17p13.1, is deleted as the result of the der(5;17).

Recent molecular studies including next generation sequencing (NGS) testing of MNs have shown that acquired mutational events that can involve *FLT3*, *NPM1*, *CEBPA*, *DNMT3A*, *IDH1*, *IDH2*, *KIT*, *MLL-PTD*, *TET2*, *RUNX1*, *ASXL1* and *TP53* are frequent in *de novo* AML or MDS and can be used for risk stratification, especially in patients with normal karyotypes (21,22). High frequency somatic mutations also have been reported as the consequence of cytotoxic therapy (23). For example, *RAS* pathway mutations have been observed in 50% of t-AML cases with –7/del(7q), suggesting a possible cooperative effect between haploinsufficiency of genes on chromosome 7 (6,24). Point mutations of *RUNX1* and *RAS* are reported to be associated with disease progression in patients with t-MNs (10) and point mutations of *TP53* represent the most frequent genetic abnormality, occurring in 20–40% of t-MNs, compared with 5–20% of *de novo* AML and MDS (9,23,25). Similar findings using NGS-based approaches also support that concept that *TP53* is commonly mutated in t-MNs, significantly more often than in *de novo* AML/MDS (23,26). However, there are very limited mutational studies conducted in MNs or t-MNs with the der(5;17).

To better understand the clinicopathological features of MNs with der(5;17)(p10;q10), we retrospectively studied 48 patients with MDS and AML including therapy-related (t-AML and t-MDS) carrying this aberration. We correlated these findings with conventional cytogenetic and molecular data and clinical outcome.

Methods

Patient inclusion

This study was approved by the institutional review board at The University of Texas MD Anderson Cancer Center (MDACC). The cytogenetic database of the Department of Hematopathology at MDACC was searched for cases with the whole-arm translocation of der(5;17)(p10;q10) detected by conventional karyotyping. From a review of 3629 AML, 2356 MDS and 1625 acute lymphoblastic leukemia (ALL) cases tested between August 2000 and March 2014, we identified 48 cases with the der(5;17) all with a diagnosis either AML or MDS. No ALL cases with the der(5;17) were identified. Only those cases with available clinical data were included in this study.

The neoplasms were diagnosed and classified according to 2008 WHO classification (27). The clinical presentation, laboratory data, bone marrow (BM) morphologic findings, immunophenotype determined by flow cytometry, and treatment and outcome were collected. Multilineage dysplasia is one of the morphologic criteria referring to cases with dysplastic features in >2 hematopoietic lineages (28,29).

Chromosome analysis

Conventional cytogenetic analysis was performed at the time of diagnosis and during the clinical follow up according to the standard laboratory procedures. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature 2013 (30).

Mutation analysis

Genomic DNA extracted from bone marrow aspirate material was PCR amplified and subjected to mutation analysis for codons 12, 13 and 61 of *KRAS* and *NRAS* by pyrosequencing using a PSQ HS 96 Pyrosequencer (Biotage, Uppsala, Sweden), or *KIT* (exons 8 and 17) and *CEBPA* by direct Sanger sequencing on an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). A fluorescence-based multiplex PCR was used to detect internal tandem duplication (ITD) and D835 point mutation of the *FLT3* gene and exon 12 of the *NPM1* gene. The PCR products were then subjected to capillary electrophoresis on an ABI Prism 3100 Genetic analyzer to distinguish wild and mutant genotypes. For a subset of the cases (n = 10), *TP53, KIT, NPM1, KRAS, NRAS, IDH1, APC, TET2* and *ASXL1* (and other genes) mutations were assessed using a next generation sequencing (NGS)-based assay and panels of either 28 or 53 genes as previously described (31). The 28-gene panel covers exons (codons) 4–10 (41–224 and 234–367) and the 53-gene panel covers exons (codons) 2, 4–8, and 10 (1–12, 69–112, 126–253, 267–206, and 332–342) for the *TP53* gene.

Statistical analyses

All data were statistically analyzed using the Statistical Package for Social Science (SPSS version 17.0). The Chi-square test, Fisher's exact test or Mann–Whitney U test was performed to compare between groups. Overall survival (OS) was measured from date of diagnosis to the date of last follow-up or death. Disease-free survival (DFS) was measured from date of complete remission (CR) to the date of relapse, last follow-up or death. The Kaplan–Meier method was used to construct survival curves the results were compared using the log-rank test. Statistical significance was considered at P value less than 0.05.