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Myelodysplasia-Related Features of Acute Myeloid Leukemia Evolving From Philadelphia-Negative Myeloproliferative Neoplasms

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Dear Editor,

The WHO 2008 classification of myeloid neoplasms lists the following three diagnostic criteria for AML with myelodysplasia-related changes (MRC): AML arising from a previously diagnosed myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MPN), AML with an MDS-related cytogenetic abnormality, and AML with multi-lineage dysplasia [1]. However, a history of Philadelphia chromosome-negative MPN (Ph-MPN) does not warrant a diagnosis of AML with MRC. Here, we demonstrate that AML evolving from Ph-MPNs (MPN-AML) has similar cytogenetic characteristics and prognosis to AML evolving from MDS or MDS/MPN (MDS-AML).

We identified 103 patients in our bone marrow archive who were diagnosed with AML that evolved from MDS (N=72), MDS/MPN (N=10), or Ph-MPN (N=21) from January 2006 to December 2014. The underlying Ph-MPNs included 13 (61.9%) cases of primary myelofibrosis (PMF), five (23.8%) of essential thrombocythemia (ET), and three (14.3%) of polycythemia vera (PV). MDS-related cytogenetic abnormalities were identified in 31 of 82 (37.8%) MDS-AML patients and in 12 of 21 (57.1%) patients with MPN-AML (P=0.175). The two most common abnormalities were a complex karyotype involving -5/del(5q) and isolated -7/del(7q) in all patients, without significant differences among patient groups (Fig. 1). Multi-lineage dysplasia was more often identified in patients with MDS-AML (28, 34.1%) than in patients with MPN-AML (2, 9.5%; P=0.031). Overall, 13 (61.9%) patients with MPN-AML were diagnosed with AML with MRC on the basis of cytogenetics or cytomorphology. Two patients with PMF received cytotoxic therapy before transformation of PMF to AML. During their progression to AML, one patient had a normal karyotype and the other had a complex karyotype, with both -5 and del(7q) already present during the PMF stage. The median overall survival (OS) and relapse-free survival (RFS) were 7.4 (5.2-9.2) and 22.5 (5.9-39.0) months, respectively, for patients with MDS-AML, and were 4.9 (1.3-11.9) and 4.0 (3.2-12.4) months, respectively, for those with MPN-AML. However, there were no differences in the OS (P=0.162) and RFS (P=0.467) between the 2 patient groups (Fig. 2A). Among the MPN-AML patients, those with MRC features had a shorter OS than those without MRC (P=0.008; Fig. 2B).

The patients with AML with MRC had significantly poorer clinical outcomes than those with not-otherwise-specified AML [2]. Similar to patients with MDS transforming to AML, a substantial proportion of PMF patients transform to AML [3]. Moreover,

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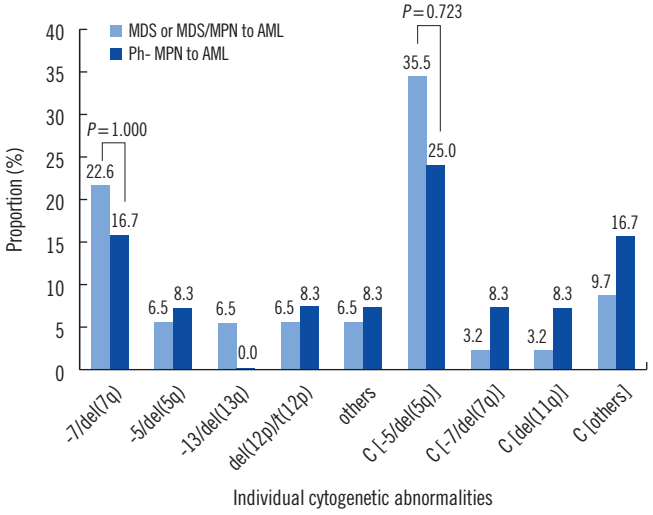

Fig. 1. The proportion and distribution of individual cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes in the study patients. No statistical differences were seen between the frequencies of -5/del(5q) in complex karyotypes and isolated -7/del(7q) in the two patient groups.
Abbreviations: MPN, myeloproliferative neoplasm; Ph-MPN, Philadelphia chromosome-negative myeloproliferative neoplasm; C, complex karyotype.

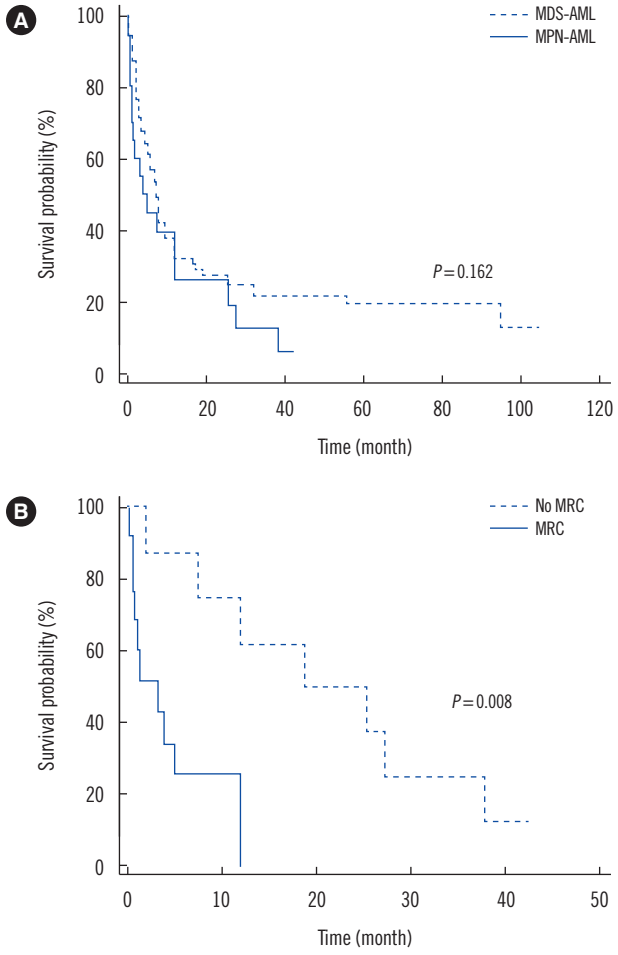

Fig. 2. Overall survival of the study patients. (A) Overall survival of patients with MDS-AML (N=82) and those with MPN-AML (N=21). There was no significant difference between overall survival rates in the 2 patient groups. (B) Overall survival of MPN-AML patients stratified by the presence or absence of MRC features. Patients with MRC features (N=13) had shorter overall survival than patients without (N=8; $P=0.008$).
Abbreviations: MPN, myeloproliferative neoplasm; MRC, myelodysplasia-related changes.

even patients with PV or ET can develop AML without an intermediate stage of myelofibrosis. The leukemic transformation in Ph-MPN is associated with a uniformly poor prognosis [3]. From this perspective, our current analysis showed that the majority of patients with MPN-AML were diagnosed with AML with MRC, mainly on the basis of cytogenetic abnormalities, and the difference between the outcomes of the patients with MDS-AML and those with MPN-AML was not significant. Our most noteworthy finding was that the cytogenetic patterns were very similar between these two patient groups. A complex karyotype with multiple chromosomal changes was the dominant cytogenetic abnormality in both groups, consistent with previous findings for patients with MPN-blast phase or AML with MRC [3-7]. Of note, a recent study reported that the involvement of del(5q) in complex karyotypes was associated with an extremely adverse prognosis in newly diagnosed MDS patients, which highlights the critical role of del(5q) as the primary event leading to chromosomal instability, susceptibility to rearrangements, and genomic damage [8]. Thus, the previously mentioned cytogenetic pattern of MPN-AML could explain, at least in part, the adverse clinical outcomes that were comparable to those of patients with MDS-AML. According to a recent epidemiologic study, secondary AML (sAML) occurring after non-MDS was associated with reduced survival across age and cytogenetic risk groups, whereas previous MDS or therapy-related AML did not impact overall outcomes among patients older than 60 yr of age and with an adverse karyotype [9]. Among patients with non-MDS-sAML, 73.8% had Ph-MPNs. These results are in line with our findings of poor outcomes for patients with MPN-AML, but suggest that the biological mechanisms involved in the leukemic transformation of Ph-MPNs to AML may be different from those involved in the transformation of MDS to AML.

Our findings indicate that the majority of patients with MPN-AML were initially diagnosed with AML with MRC, and these patients showed cytogenetic distributions and clinical outcomes similar to those with MDS-AML. From a clinical viewpoint, these findings suggest that patients with MPN-AML or MDS-AML re-

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quire therapeutic modalities different from those with *de novo* AML, in order to improve their outcomes.

Authors' Disclosures of Potential Conflicts of Interest

No conflicts of interest relevant to this article were reported.

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