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The evolving role of genomic testing in assessing prognosis of patients with myelodysplastic syndromes

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A B S T R A C T

The introduction into routine hematology-oncology clinical practice of molecular genetic testing assays based on next-generation sequencing platforms is prompting reassessment of the importance of molecular assay results in comparison to existing disease-specific risk stratification tools based on clinical assessment and light microscopy. For patients with myelodysplastic syndromes (MDS), the most commonly used tools for prognostication currently include the International Prognostic Scoring System (IPSS) and the Revised IPSS (IPSS-R), which are based on marrow blast proportion, number and degree of cytopenias, and the metaphase karyotype. Integration of DNA sequencing data into an existing evidence-based practice approach inclusive of the IPSS or IPSS-R may be challenging, but the additional information provided by molecular genetic testing clearly can influence clinical decisions, such as determining patients' eligibility for clinical trials of novel targeted agents or helping assess which patients should be referred for allogeneic hematopoietic stem cell transplantation. This review discusses the prognostic and predictive value of mutation testing in the context of current clinical care of patients with MDS.

1. Introduction

Clinicians who care for patients with myelodysplastic syndromes (MDS) are well accustomed to using the standard clinical-pathological risk stratification tools available for these difficult clonal marrow failure states, especially the 1997 International Prognostic Scoring System (IPSS) and the 2012 Revised IPSS (IPSS-R) [1,2]. The limitations of the IPSS and IPSS-R are certainly well recognized. For instance, the IPSS and IPSS-R are only validated for adult patients with de novo MDS treated without disease-modifying agents, and these systems do not capture certain clinically relevant prognostic factors such as comorbidity severity or performance status [3]. However, despite such limitations, the IPSS and IPSS-R have played a crucial role in determination of patients' eligibility for clinical trials, construction of drug approval labels, preparation of clinical guidelines such as those of the National Comprehensive Cancer Network and the European LeukemiaNet, and risk stratification of patients who could be considered for intensive therapy or allogeneic hematopoietic stem cell transplant (SCT) [4–6].

The most frequently detectable actionable molecular genetic changes seen in acute myeloid leukemia (AML)— ie, *FLT3* internal tandem duplications or juxtamembrane domain point mutations, and C-terminal *NPM1* mutations—are rarely observed in MDS, and until recently molecular findings were not known to influence the effectiveness of any of the available

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MDS therapies. As a result, molecular testing was only rarely used in the evaluation of patients with MDS before 2013. Instead, metaphase karyotyping, the results of which are captured by the IPSS and to a greater extent by the IPSS-R, provided the only genetic information routinely used in risk stratification or treatment selection (eg, lenalidomide for lower-risk patients with deletion of chromosome 5q) in the clinic [7].

The advent of next generation sequencing approaches has contributed to discovery of more than 40 recurrently mutated genes associated with MDS since 2009, many of which have prognostic importance or identify subsets of patients with a specific disease biology [8–10]. Increasingly, molecular data from Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory assays are available to front-line clinicians, which has contributed to a re-evaluation of the role of molecular genetic testing in risk stratification of patients with MDS, as well as the potential for molecular results to aid in diagnosis and treatment selection [11,12].

1.1. Incorporation of molecular genetic results into risk stratification of patients

In 2011 Rafael Bejar and colleagues presented results from primary samples from 439 patients with MDS that had been Sanger-sequenced for mutations in 18 different genes [13]. The investigators found that 5 specific genes, when mutated, provided IPSS-independent prognostic value: *TP53, ETV6, ASXL1, EZH2,* and *RUNX1.* All 5 were adverse markers, and a somatic mutation in any one of these genes effectively escalated the patient's IPSS risk by one risk category. For instance, a patient with IPSS intermediate 1 risk disease and an *ASXL1* mutation had a median survival comparable to a patient with IPSS intermediate 2 risk disease without any of the 5 high-risk mutations.

Although this ground-breaking study received considerable attention and was published in the *New England Journal of Medicine*, only 51% of patients had mutations, lower than the proportion (>75%) with detectable somatic mutations in subsequent series [8,14]. In addition, the patients in the 2011 study came from a limited number of centers, all of which were located in the United States. Furthermore, the study preceded the 2012 publication of the IPSS-R, which better stratified patients by including depth of cytopenias in the risk assessment tool, and also rebalanced the prognostic weight of adverse cytogenetics compared to cytopenias and marrow blast proportion.

Since the Bejar et al. study was published, several single institution prognostic studies have been reported, and a large international effort has been ongoing under the auspices of the International Working Group for MDS Molecular Prognosis (MDS IWG-PM) committee to assess the value of mutation testing in MDS risk stratification. Initial findings from the MDS IWG-PM study were presented at the 2015 annual meeting of the American Society of Hematology, but have not yet been published in final form [15]. Those initial results included sequencing data from 1996 patients of 17 genes including *ASXL1, CBL, DNMT3A, ETV6, EZH2, IDH1, IDH2, JAK2, KRAS, NRAS, RUNX1, SRSF2, TET2, TP53, U2AF1,* and *SF3B1*. The IWG-PM investigators found that a mutation in any one of 4 high-risk genes—*TP53, RUNX1, EZHA2, NRAS*—provided IPSS-R-independent prognostic information, similar to the 5 genes in the 2011 study. *CBL* and *U2AF1* were also adverse markers in the IWG-PM study, but just missed the $P < 0.05$ statistical significance cutoff in a multivariable analysis. The gene *SF3B1*, which encodes a spliceosome component, is frequently mutated in patients with ring sideroblasts, and which several groups had associated with a relatively indolent biology, was associated with an IPSS-R independent favorable outcome when mutated [16,17]. In contrast, a single-institution study restricted to patients with ring sideroblasts found no additional prognostic value from *SF3B1* mutation testing [18].

1.2. Molecular genetic results and their predictive value

In terms of forecasting the natural history of MDS, molecular genetic testing can provide crucial information beyond that obtained from the IPSS and IPSS-R. However, it would be helpful if mutation testing could also provide predictive value with respect to response to specific therapies.

Several groups have assessed defined cohorts of patients treated with particular drugs in order to detect whether mutation testing predicted response to those drugs (Table 1). Multiple groups observed that MDS patients with *TET2* mutations have a greater likelihood to respond to the DNA hypomethylating agents azacitidine or decitabine than those who are *TET2* wild-type [19–21]. In contrast, *ASXL1* mutations predict a lower likelihood of response to hypomethylating agents in MDS and probably also in chronic myelomonocytic leukemia [19,22,23]. Despite this observation, the difference in response rates between patients who are *TET2* or *ASXL1* wild-type or mutant are relatively small and therefore unlikely to influence clinical decisions

Table 1
Predictive value of negative testing result (no mutations) on molecular genetic panels for myelodysplastic syndromes.

Number of patients tested	Number of genes examined	Proportion of patients with confirmed mutations	Reference
439	18	51.5%	Bejar R et al. *NEJM* 2011; 364 (26):2496-506.
1996	17	80.8%	Bejar R et al. Abstract#907 ASH 2015 annual meeting
748	111	74%	Papaemmanuil E et al. *Blood.* 2013 Nov 21; 122 (22):3616-27
91	22	91%	Kwok B et al. *Blood* 2015 Nov 19; 126:2355-61

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