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Does mutational burden add to other prognostic factors in MDS?

Aziz Nazha[a,b,*]

[a] Department of Hematology and Medical Oncology, Cleveland Clinic, Taussig Cancer Center, OH, USA
[b] Center of Clinical Artificial Intelligence, Cleveland Clinic, OH, USA

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ABSTRACT

Myelodysplastic syndromes (MDS) are clonal bone marrow disorders characterized by complex genomic abnormalities that define disease phenotype, prognosis, and progression. The overall outcomes of MDS patients are very heterogeneous and can be measured in months in some patients and years in others. Several scoring systems have been developed in MDS, with the International Prognostic Scoring System (IPSS) and its revised version (IPSS-R) the most widely accepted risk stratification tools in clinical practice and trial eligibility. Recently, somatic mutations have been shown to impact overall survival and the risk of progression to acute myeloid leukemia. Attempts to add this information to current models or develop newer models are underway, but the optimal approach remains controversial. Newer methods to develop a personalized prediction model that provides outcomes specific for a patient were developed and could change the prognostic paradigm for MDS patients in the near future.

Introduction

Myelodysplastic syndromes are a group of clonal disorders characterized by evidence of dysplastic features in the bone marrow and manifest as cytopenias and increased risk of acute myeloid leukemia transformation (AML) [1]. The outcomes of MDS patients are variable and significant heterogeneity exists in the disease course and response to current therapies. Accurate prediction of the patient outcomes is important clinically and can guide appropriate treatment selection.

Several scoring systems have been developed to stratify MDS patients, with the most commonly used systems in clinical practice and trials eligibility including the International Prognostic Scoring System (IPSS) and its revised version IPSS-R [2–6]. All these models use clinical variables with different cutoffs and prognostic impact. Recent advancement in genome sequencing technologies have described the molecular landscape and identified several mutations that have an independent impact on MDS outcomes [7–12]. Attempts to incorporate this data into current models or build new models that use clinical and mutational data are currently underway.

In this article, we discuss the impact of somatic mutations on outcomes in MDS and review the attempts to incorporate this information into current prognostic models. We also review attempts to build a personalized prediction model that can use clinical and genomic data to predict individual risk.

* Lerner College of Medicine, Case Western Reserve University, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Desk CA6 9500 Euclid Ave, Cleveland, OH, 44195, USA.
E-mail address: nazhaa@ccf.org.

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Table 1
Impact of commonly mutated genes in MDS on overall survival.

Mutated Gene	Frequency	Impact on overall survival
TET2	20%–30%	Neutral
SF3B1	20%–25%	favorable
ASXL1	15%–20%	Controversial, Adverse in some studies
SRSF2	10%–20%	Controversial, Adverse in some studies
DNMT3A	10%–15%	Neutral
RUNX1	~10%	Adverse
U2AF1	< 10%	Neutral
EZH2	5%	Adverse
TP53	5%–10%	Adverse
IDH1/IDH2	< 10%	Neutral

Clinical prognostic models in MDS

The most widely accepted models in MDS include IPSS, IPSS-R, the WHO Prognostic Scoring System (WPSS), and the Global MD Anderson Prognostic Scoring System (MDAPSS) [2–6]. All these models use variables such as bone marrow biopsy blasts percentage, cytogenetic analysis, and degree of cytopenias, and some of them add other prognostic factors such as age and transfusion dependency. The IPSS and IPSS-R are the most commonly used models in clinical practice, guidelines, and clinical trial eligibility.

Several shortcomings have been recognized when applying these models in clinical practice, including less predictability of the IPSS and IPSSR in patients with therapy-related and secondary MDS, the reduction of the accuracy of the model when applied over time during the disease course, and the lack of predictability of outcomes after hypomethylating agent failure [13].

Prognostic impact of somatic mutations in MDS patients

Several well designed studies that have used next generation target deep sequencing and whole exome sequencing have highlighted the genomic landscape of MDS [7–12]. These studies have shown that approximately 80%–90% of samples from MDS patients will have one or more somatic mutations when a genomic panel of approximately 30–40 genes is included. It also showed that approximately 10–12 of these mutations are present in 5% or more patients, which means that the majority of these mutations occur in very low frequency [7–12]. This is very important, as some of these low-frequency mutations could have prognostic or biological impact on the disease course and response to therapy. But this impact can be labeled as not significant using traditional statistical methods, given the small number of patients included in the analysis. Further, these studies have shown that some of these somatic mutations have a significant impact on overall survival (OS) and AML transformation risk that is independent from other prognostic variables (Table 1) [7–12]. The prognostic impact of molecular data can be recognized in two ways: the independent impact of a single mutation on outcomes, and the impact of the number of mutations (mutations load) on OS and AML transformation (higher number of mutations correlates with worse OS and higher risk of AML transformation) [7–12].

The significant impact of single gene mutations on OS and AML transformation have been demonstrated in several studies that used different sized patient cohorts and different numbers of genes in their panel. Mutations such as *TP53*, *EZH2*, *RUNX1*, and *SF3B1* have frequently shown to independently impact overall survival in several studies, while others such as *ASXL1*, *TET2*, *DNMT3A*, *SRSF2*, *U2AF1* and others have been controversial (Table 1) [7–12]. The difference in the results of these studies could be related to the sample size, the number of genes included in the analysis, and the statistical/bioinformatics methods. More importantly, these studies have shown that the prognostic impact of certain genes could be significant in some clinical context while not significant in others. In a large study of 3562 MDS samples collected from an international database, univariate analysis showed that *TP53*, *RUNX1*, *EZH2*, *NRAS*, *SF3B1*, *CBL, ASXL1*, *TET2 IDH2, KRAS*, and *NPM1* mutations have statistically significant impact on OS, but this impact could change based on blast cutoff [8]. For example, mutations in *ASXL1*, *U2AF1*, and *SRSF2* have a negative impact on OS in patients with blast percentages < 5% but lose their independent significance in patients with higher blast percentages [8]. However, in multivariate analyses that included significant mutations and the IPSS-R scoring system, 5 mutations remained significant (*TP53*, *RUNX1*, *EZH2*, *NRAS*, and *SF3B1)*. This analysis did not adjust for age, which may change the prognostic impact of some of these mutations.

Several attempts have been made to add mutational data to current existing models or build a new geno-clinical model, yet the optimal approach to use this data clinically in the prognosis of MDS patients remains a work in progress.

How can we incorporate mutational data into current prognostic models?

Given the independent prognostic impact of some somatic mutations that can be potentially additive to clinical data, several studies have tried to add mutational data to current models. Bejar et al. evaluated 439 MDS patients for the presence of 18 gene mutations. In a multivariable Cox regression model, the presence of mutations in five genes retained independent prognostic significance: *TP53* (hazard ratio, 2.48), *EZH2* (hazard ratio, 2.13; 95% CI), *ETV6* (hazard ratio, 2.04), *RUNX1* (hazard ratio, 1.47), and *ASXL1* (hazard ratio, 1.38) [7]. The presence of one or more of these mutations can upgrade the risk category of a patient to higher

risk. For example, the median OS for a patient with low risk by the IPSS scoring system can be similar to OS of a patient in the intermediate-1 risk group if this patient has one or more of these mutations [7]. In another study of 508 MDS patients treated at the Cleveland Clinic, only mutations in *SF3B1*, *RUNX1*, *TP53*, *EZH2*, and *NPM1* had an independent impact on OS in univariate analysis. However, only three of these mutations, *EZH2*, *SF3B1*, and *TP53*, remained significant after adjustment for age and risk scoring according to the IPSS-R [10]. A linear risk score was developed based on the Beta coefficient of each of these factors: age x 0.04 + IPSS-R score x 0.3 + *EZH2* x 0.7 + *SF3B1* x 0.5 + *TP53* × 1 [10]. The new model outperformed IPSS-R in its predictability (higher concordance index) for OS and AML transformation and also improved the predictability of IPSS-R when applied to paired samples with available clinical and mutational data at different times during the disease course [10]. To develop an easier scoring system for use in the clinic, the authors attempted to add mutational data to all established prognostic models in MDS. Similar to previous analyses, mutations in *EZH2*, *TP53*, *RUNX1*, *NPM1*, and *SF3B1* had a significant impact on OS in univariate analysis and only three mutations, *EZH2*, *TP53*, and *SF3B1,* remained significant after adjustment for clinical variables [9]. The investigators developed a simplified scoring system that can add the mutations by assigning a score to each one of them that can be added to the actual model score [9]. More importantly, adding mutations to all existing models can upstage and downstage patients into different risk categories that reflects their actual risk. For example, adding molecular data to the IPSS-R scoring system could upstage 26% of patients with lower-risk disease to a higher-risk category including 62% of patients with intermediate-risk disease [9].

Other studies have attempted to build a mutations-only model. In an analysis of 944 MDS patients, Haferlach et al. included 14 mutations, age, gender, and other clinical variables to build a new prognostic model. The authors built gene-only and geno-clinical models [12]. The geno-clinical model outperformed bother the gene-only model and the IPSS-R, suggesting that despite the significant overlap between clinical and genomic data, some clinical variables retain prognostic impact that is independent of mutational data [12].

Impact of mutation characteristics

Current attempts to evaluate the prognostic impact of somatic mutations have only considered the presence or absence of these mutations and did not take into account mutation characteristics such as the functional consequences of a mutation, variant allelic frequency (VAF), type of mutation (missense vs others). Evidence suggests that this information could add to the prognostic impact of some mutations. In a study of 732 MDS patients, 73 (10%) had *TP53* mutations [14]. *TP53* mutations were defined as drivers in 20% of samples, 40% as passenger, and 40% as mosaic. Mutation positions included: 19 (24%) in the DNA binding domain, 2 (3%) in the transactivation domain, 1 (1%) in the tetramerization domain, and 58 (72%) other [14]. Patients with *TP53* as driver mutations had a worse OS compared with patients with *TP53* as passenger mutations (median, 2.2 vs 13.0 months, respectively, $P = .02$). Similarly, OS by *TP5*3 VAF as low (< 25%), intermediate (25%–50%), and high (> 50%) was 12.4, 8.5, and 3.4 months, respectively [14]. In another study of 621 patients with MDS and other myeloid malignancies, *BCOR* mutations did not have any independent prognostic impact on OS and AML transformation even after controlling for clinical variables [15]. However, mutation characteristics did have an impact on OS. For example, the median OS for patients with frameshift mutations was 10.9 months compared to 50.4 months for patients with other types of mutations ($P = .03$) [15]. The median OS for patients with mutations occurring in the binding domains was 10.6 months compared to 38.8 months for mutations outside of the binding domains. All this data suggests that mutation characteristics may have an important prognostic impact on MDS outcomes.

Should future prognostic models provide personalized prediction?

It is evident that our current models can underestimate or overestimate the risk of individual patients and can underestimate the degree of heterogeneity of outcomes in MDS patients. In an attempt to build a model that uses clinical and genomic data and can provide a personalized outcome that is patient specific, a multicenter cohort of 2302 MDS patients were used to build and validate the model [16]. The investigators used a random survival forest model (a machine learning model) to build the new model in which clinical and molecular variables are randomly selected for inclusion in determining survival, thereby avoiding the shortcomings of traditional Cox step-wise regression in accounting for variable interactions [16]. The machine learning algorithm identified the following variables that impacted OS: cytogenetic risk categories by IPSS-R, platelets, mutation number, hemoglobin, bone marrow blasts %, 2008 WHO diagnosis, white blood cell (WBC) count, age, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), *TP53*, *RUNX1*, *STAG2*, *ASXL1*, absolute monocyte counts (AMC), *SF3B1*, *SRSF2*, *RAD21*, secondary vs de novo MDS, *NRAS*, *NPM1*, *TET2*, and *EZH2*. The C-index for the new model was 0.74 for OS and 0.81 for AML transformation. The new model outperformed IPSS (c-index 0.66, 0.73) and IPSS-R (0.67, 0.73) for OS and AML transformation, respectively [16]. This approach suggests that we could provide personalized prediction that is specific for a given patient that may change their overall outcomes.

Conclusions

Our current prognostic models in MDS have been very useful tools in treating MDS patients and provide a staging tool for clinical trials eligibility, however several challenges remained when these models were applied in practice. Genomic data have an important prognostic impact that can be additive to other prognostic variables, though the optimal way to incorporate this information in a widely accepted model remains a work in progress. Personalized prediction models can provide individualized outcomes that are patient-specific and may help in providing personalized treatment plans in the future.

Disclosures

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