Clinical and genetic predictors of prognosis in myelodysplastic syndromes

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ABSTRACT

Myelodysplastic syndromes are a collection of clonal hematopoietic disorders with a wide range of clinical manifestations and eventual outcomes. Accurate prediction of a patient's prognosis is useful to define the risk posed by the disease and which treatment options are most appropriate. Several models have been created to help predict the prognosis for patients with myelodysplastic syndromes. The International Prognostic Scoring System (IPSS) has been the standard tool used to risk stratify MDS patients since its publication in 1997. Other models have since been created to improve upon the IPSS, including the recent Revised International Prognostic Scoring System. Most models include the presence or severity of peripheral blood cytopenias, the proportion of bone marrow blasts, and specific karyotype abnormalities. Other factors including age, performance status, co-morbidities, transfusion dependence, and molecular biomarkers can further refine the prediction of prognosis in some models. Novel, disease specific biomarkers with prognostic value in myelodysplastic syndromes including cell surface markers, gene expression profiles, and high resolution copy number analyses have been proposed but not yet adopted clinically. Somatic abnormalities in recurrently mutated genes are the most informative prognostic biomarkers not currently considered by clinical risk models. Mutations in specific genes have independent prognostic significance and, unlike cytogenetic abnormalities, are present in the majority of myelodysplastic syndrome cases. However, mutational information can be complex and there are challenges to its clinical implementation. Despite these limitations, DNA sequencing can refine the prediction of prognosis for myelodysplastic syndrome patients and has become increasingly available in the clinic where it will help improve the care of patients with myelodysplastic syndromes.

Introduction

Accurately predicting the prognosis once a malignancy has been diagnosed is of great importance to both patients and their physicians alike. This is certainly true when that malignancy is one of the myelodysplastic syndromes (MDS) since clinical outcomes for patients with MDS can vary greatly, even between those considered to have the same disease subtype. Therefore, clinical models that help physicians predict prognosis have become a cornerstone of MDS care. Over time, these models have grown in both accuracy and complexity, reflecting new knowledge about disease risk and patient features that contribute to outcomes.[1] Advances in our understanding of the genetic basis of MDS stand poised to further refine our ability to predict how individual patients are likely to be impacted by their disease. This review will describe recent changes to prognostic models, highlighting their strengths and potential weaknesses, and explore how molecular genetics might be used clinically to further individualize the care of patients with MDS.

To begin, it is useful to highlight how the prediction of prognosis is valuable in MDS. From a patient's perspective, the prognosis helps define the severity of disease and sets expectations as to how it is likely to impact them. Patients often want to know "how much time they have left". To accurately individualize this estimate requires consideration of the whole patient: their disease, their comorbidities, their age, and, potentially, even their socio-economic status. Treatment options and likelihood of response would weigh heavily in this discussion. In contrast, prognostic information from a physician's standpoint is essentially a means of staging the disease in a manner that can be used to help direct therapy. The relevant prognosis in this case focuses primarily on disease-specific risk, and in particular, the risk of progression or death in the absence of therapy. This risk is weighed against the likely benefits and potential toxicities of specific treatments.

For both patients and physicians, the estimation of prognosis is a continual process that does not happen just at the time of diagnosis. Reevaluating the prognosis may be useful when a patient shows signs of progression or after they have become refractory to standard treatment. Prognostic models that consider features present before the administration of a specific therapy would also be very valuable, particularly if they identified subsets of patients whose prognosis is significantly improved by a particular treatment.

No one prognostic model can satisfy the needs of patients and physicians in every conceivable context while maintaining accuracy. Different systems may be useful in distinct scenarios or patient subgroups. Scoring systems used to describe subjects in clinical trials or that are incorporated into clinical practice guidelines have the greatest utility. Historically, the International Prognostic Scoring System (IPSS) has met this need. Its revision, the IPSS-R, improves upon the IPSS and is becoming the *de facto* standard for determining MDS prognosis. However, none of the widely adopted prognostic models currently considers molecular genetic abnormalities. Somatic mutations represent the pathogenic events responsible for

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MDS development and progression and can be found in nearly every MDS patient. Mutations have strong associations with clinical phenotypes and outcomes, making them ideal prognostic biomarkers. This review will examine the challenges associated with interpreting mutation information and how these obstacles are being overcome to improve risk stratification for patients with MDS.

Clinical prognostic models in myelodysplastic syndromes

IPSS and IPSS-R

The IPSS was published by the International Myelodysplasia Risk Analysis Workshop in 1997 and became a standard for the prediction of prognosis in MDS patients.[2] The model was simple to use in that it only considered three variables: karyotype abnormalities, the percentage of blasts in the bone marrow, and the number of cytopenias present. All of the information needed to calculate the IPSS was available as part of the standard diagnostic evaluation. Patients were stratified into one of four risk groups with meaningful differences in overall survival. Clinical trials that led to the approval of many standard MDS therapies used the IPSS to describe patients in their studies and practice guidelines like those published by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) define their treatment algorithms by IPSS risk groups[3,4] This has led to the widespread adoption of the IPSS by academic and community practioners alike. However, the IPSS has several perceived shortcomings. First, it was created by examining patients only at the time of diagnosis and only followed prior to receiving any disease-modifying therapy. Second, the IPSS does not consider the severity of cytopenias, only their presence, and thereby likely underestimates disease risk in many patients without other adverse features such as excess blasts or adverse karyotypes. Finally, in 2001 the World Health Organization (WHO) reclassified the presence of 20-30% bone marrow blasts as acute myeloid leukemia essentially removing this category of patients considered by the IPSS.[5,6]

The revision to the IPSS (IPSS-R) was published in 2012 and addresses several of these shortcomings.[7] The IPSS-R was created by examining data from 7012 MDS patients who were censored if and when they received disease-modifying therapy. The final IPSS-R model includes the same major categories as the IPSS, but with significant changes to each, as shown in Figure 1.[8] Cytogenetic risk groups are more heavily weighted and have been expand-

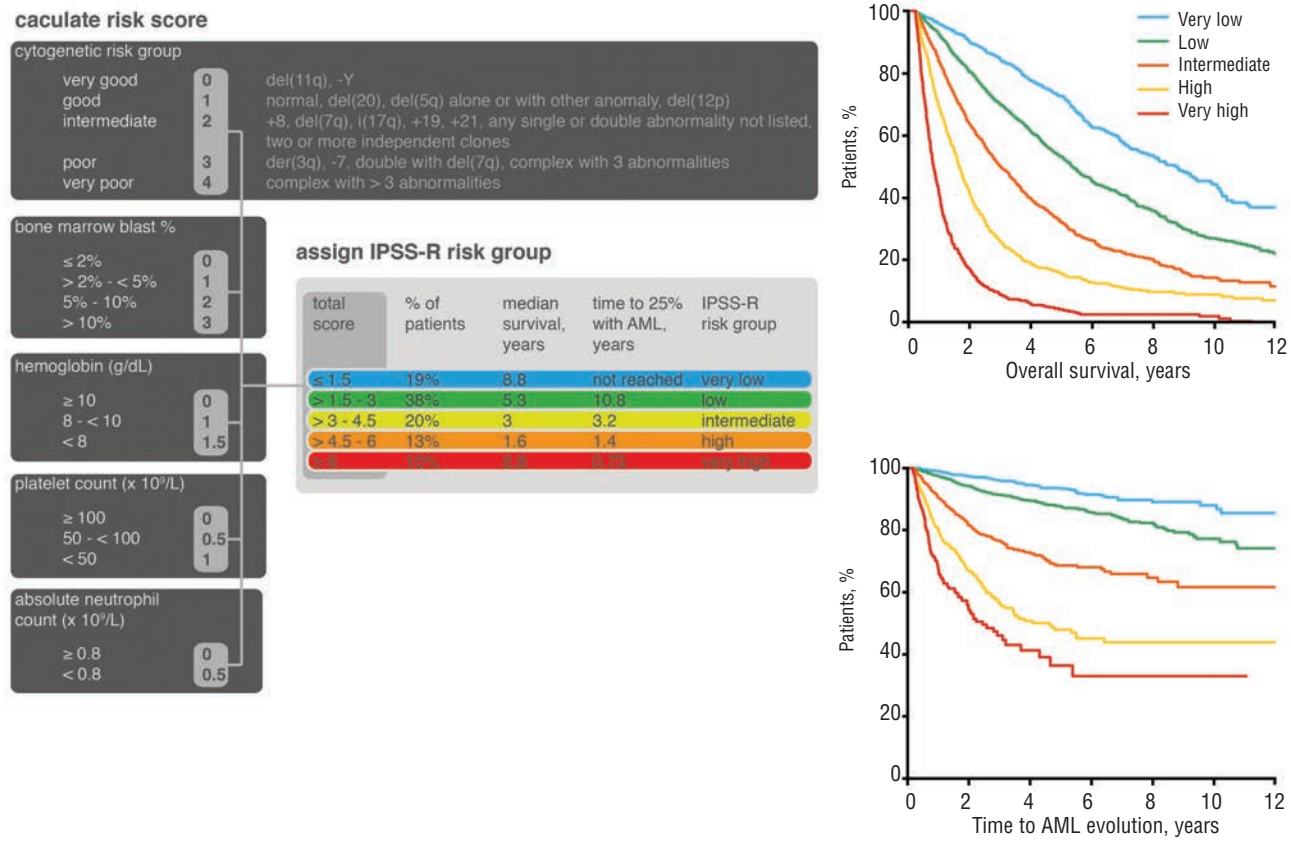

Figure 1. International Prognostic Scoring System Revised (IPSS-R). Karyotype abnormalities, bone marrow blast proportion, and severity of peripheral blood cytopenias are scored and used to assign MDS patients into one of five risk groups with significant differences in median survival and probability of developing AML. The cut offs shown for the 5 risk groups can be adjusted for age. The values shown here are for 70-year old patients. This figure is adapted from Steensma DP.[8] (Copyright American Society of Hematology, used with permission).

ed to include nearly three times as many specific abnormalities. The relative weight of bone marrow blast percentage has been refined by eliminating the 21-30% category and recognizing that as few as 3% blasts add risk. Finally, each peripheral cytopenia is considered separately and additional risk is assigned for greater severity. Age-adjusted cut offs are used to assign patients to one of five risk groups instead of the four used by the IPSS. Several independent validations of the IPSS-R have now been reported in a wide variety of contexts. These include patient populations that were not considered in the creation of the IPSS. For example, the IPSS-R has been validated at times other than diagnosis, in patients treated with lenalidomide, in patients treated with hypomethylating agents, and in patients receiving a stem cell transplant.[9-13] It is important to note that while the IPSS-R can risk stratify patients in these scenarios, the median survival estimates published with the IPSS-R may not be accurate in these contexts. Validation studies comparing prognostic models suggest that the IPSS-R appears to outperform the IPSS and WPSS in these broader contexts.[11,12,14]

Additional models

Before the publication of the IPSS-R, several other prognostic models were created to improve the prediction of prognosis in patients with MDS. The World Health Organization (WHO)-based prognostic scoring system (WPSS) combines WHO-defined MDS subtypes with cytogenetic abnormalities and the presence of severe anemia to stratify patients into one of five risk groups. The WPSS is dynamic in that it has been shown to be valid at times other than diagnosis and is included in MDS practice guidelines.[15]

Researchers at MD Anderson created two different prognostic models for MDS. The first is a lower risk prognostic scoring system (LR-PSS) that is designed to better risk stratify patients with Low or Intermediate-1 risk as defined by the IPSS. The LR-PSS adds age and the severity of thrombocytopenia to assign MDS patients into one of three risk categories.[16,17] Nearly one-third of patients predicted to have lower risk disease by the IPSS fall into the highest risk category of the LR-PSS, a group with a median survival that is comparable to that of the IPSS Intermediate-2 risk group. This model has subsequently been validated in independent cohorts.[17,18] The LR-PSS highlights how the IPSS underestimates risk in a significant number of cases and demonstrates the greater sensitivity that can be achieved by focusing on a patient subpopulation. Models designed specifically for patients with chronic myelomonocytic leukemia (CMML) have utilized this approach including the recently validated CMML-prognostic scoring system.[19-21]

The second independently validated MD Anderson model is a comprehensive scoring system (CSS) that is designed to be more inclusive, but at the price of added complexity.[22,23] The CSS considers patient populations not included in the IPSS and IPSS-R, such as those with therapy-related MDS, proliferative CMML, and recipients of prior therapy. In addition to features considered by the IPSS, it includes age as an explicit variable, total WBC count, thrombocytopenia severity, and Eastern Cooperative Group (ECOG) performance status.[22] The CSS can re-stratify patients assigned to risk groups by the IPSS and does not require additional laboratory testing. However, its perceived complexity may be a barrier to its widespread adoption.

Consideration of non-disease features

By including age and ECOG performance status, the CSS captures important patient information that may not be related to their MDS. This is valuable for predicting an accurate prognosis, although it confounds longevity with disease-specific risk. For patients, an estimate of expected lifespan is clearly important. For physicians, disease risk is more useful for selecting among therapeutic options. Non-disease measures such as performance status and comorbidities are typically taken into account by physicians, but in a less formal manner. Several prognostic models have quantified the contribution of non-disease, patient-specific measures on survival.[24] Such studies demonstrate prognostic value of these measures, particularly in patients predicted to have lower risk MDS. For example, the MDS-Specific Co-morbidity index and the Adult Comorbidity Evaluation-27 instrument show independent prognostic value when combined with the WPSS or IPSS, respectively.[25,26] Similarly, the Hematopoietic Cell Transplantation (HCT) Comorbidity Index is useful to predict HCT-associated risks and has been specifically validated in MDS patients.[27-29]

Additional prognostic features

Additional biomarkers such as albumin, marrow fibrosis, ferritin, and LDH levels have been shown to have prognostic significance. Ferritin and LDH levels can add to the IPSS and were considered for inclusion in the IPSS-R.[7,30] While not in the final model, these measures are recommended for refining prognosis in Intermediate risk group patients who straddle the boundary between higher and lower risk categories.[3]

Molecular genetics as prognostic biomarkers

Prognostic biomarkers derived directly from tumor cells may be more precise predictors of disease specific risk. Karyotype abnormalities are tumor-derived biomarkers considered in current prognostic models, but are present in less than 50% of cases. In the IPSS-R, two-thirds of patients fall into the 'Good' cytogenetic risk category and are essentially not stratified by this measure. Other tumor specific biomarkers with prognostic significance include flow cytometry, gene expression profiling, and genome-wide copy number analyses.[31,32] While promising, these tests have important technical limitations and have not been adopted as routine elements of care due to their complexity and lack of clinical access. Attempts to standardize their performance and interpretation will help these measures gain clinical acceptance in the future.[33-35]

In contrast, the identification of disease-associated somatic mutations is more straightforward and there is increasing evidence to support their use as prognostic biomarkers (Table 1). Advances in DNA sequencing have been used to discover a large number of genes mutated in patients with MDS. Well over 40 are known to recurrently carry somatic mutations and more than 80% of patients will have at least one such genetic abnormality. The genes altered by mutation are involved in a wide range of oncogenic and biologically important pathways including epigenetic regulation, RNA splicing, growth factor signaling,

transcriptional regulation, apoptosis, and genomic stability.[36] As such, somatic mutations identify relevant, disease-associated pathways making them more direct markers of the abnormal biology that gives rise to the disease phenotype.[37] To date, 3 major studies have examined the impact of recurrently mutated MDS genes on overall survival in large cohorts of patient samples.[17,38-40] These studies conclusively show the strong association between mutations in specific genes and disease risk. They also explore the complex genetic landscape of MDS, highlighting the challenges that must be overcome before this information can best be used to direct the care of patients.

Challenges of molecular genetic biomarkers in MDS

Determining how best to combine clinical and genetic information has been one of the major obstacles to the adoption of routine sequencing in clinical practice.

Many mutated genes have been associated with differences in overall survival. For example, mutations of *NRAS, RUNX1, ASXL1, EZH2, TP53, ETV6, DNMT3A, U2AF1*, and several others, can identify patients with a poorer prognosis than their unmutated counterparts. As with cytogenetic abnormalities, the more mutations patients carry, the more likely they are to have advanced disease and a higher predicted risk of death or transformation to AML (Figure 2).[38-40] However, somatic mutations are also determinants of classic MDS risk factors such as bone marrow blast proportion, peripheral cell counts, and even genomic instability.[37,38] Therefore, clinically-based prognostic models capture much of the prognostic significance that might otherwise be associated with somatic mutations. As a consequence, not all mutated genes have prognostic significance that is independent of these more clinically accepted biomarkers. For example, NRAS mutations are strongly associated with excess bone marrow blasts and severe thrombocytopenia.[38] When these features are controlled for, the presence of a conventionally identified NRAS mutation does not add predicted risk. Both Papaemmanuil *et al.*[39] and Haferlach *et al.*[40] have shown that comparisons of mutation-based prognostic models are not significantly inferior to models that include more standard clinical risk factors. Mutations may be a more precise way of assessing such risk since clinical measures such as blast proportion and cytopenias may be more subjective or likely to vary over time. Nevertheless, mutations by themselves are unlikely to

Table 1. Frequent genetic abnormalities in myelodysplastic syndromes.

Cytogenetic abnormalities	Approximate frequency	Disease associations	Associated risk
der(3q)	1%	Often rearrangements near *EVI1-MDS1* locus	Poor
del(5q)	7%	Isolated: anemia, normal to elevated platelet count, but often part of complex karyotype	Good
del(7q)	1%	Often part of complex karyotype	Intermediate
del(11q)	1%		Very Good
del(20q)	2%	Common in other myeloid malignancies	Good
Trisomy 8	5%	Rare autoimmune or aplastic features, common in other myeloid malignancies	Intermediate
Deletion 7	2%	Often part of monosomal karyotype	Poor
Deletion Y	2%		Very Good
3 abnormalities	2%		Poor
>3 abnormalities	7%	Monosomal karyotype, TP53 mutation	Very Poor
Single gene mutations	**Approximate frequency**	**Disease associations**	**Associated risk**
TP53	8%	Complex and monosomal karyotype, excess blasts, thrombocytopenia, few mutations in other genes	Very Poor
SF3B1	20-30%	Ring sideroblasts, fewer mutations in other genes	Good
SRSF2	15%	More common in CMML	Poor
U2AF1	10%	Often with del(20q)	Poor
ZRSR2	5%	On X-chromosome, more common in males	Neutral
TET2	20-30%	Normal karyotype, monocytosis, more frequent in CMML	Neutral
DNMT3A	10-15%		Poor
ASXL1	15-20%		Poor
EZH2	5%	More common in CMML	Poor
RUNX1	5-10%	Thrombocytopenia, excess blasts	Poor
ETV6	2%		Poor
NRAS/KRAS	5-10%	Thrombocytopenia, excess blasts, monocytosis, more common in CMML, often subclonal	Poor
JAK2	5%	50% of RARS-T, often subclonal	Neutral
CBL	5%	Monocytosis, excess blasts, more common in CMML	Poor
IDH1/IDH2	5%		Mixed evidence

capture all disease relevant risk factors. In general, combining clinical features to mutational information have been shown to improve prognostic models by a small margin.[39,40] Mutations may be more significant in specific subsets of patients or certain clinical scenarios.

There are other challenges facing the clinical interpretation of somatic MDS mutation data. For example, there do not appear to be many tight, genetically defined MDS subtypes. The prognostically favorable isolated del(5q) group is the only genetically defined MDS subtype in the WHO classification. But even there, prognostic variability exists as some patients may have larger 5q deletions or *TP53* mutations, both of which have been shown to be prognostically adverse.[41-43] The clinical heterogeneity associated with MDS is further reflected in the various patterns of mutation observed in patients. Most of the recurrently mutated genes can overlap with each other, although examples of mutual exclusivity or apparent cooperativity between mutations have been identified. This variability makes it difficult to discern how co-existing mutations should be considered. Are their respective risks combined or do certain mutations override the importance of others, allowing these to be ignored if present? To add to this complexity, most MDS-associated genes are mutated in only a small minority of patients. Of the 30 or so recurrently mutated genes identified in Papaemmanuil *et al.*[39] and Haferlach *et al.*,[40] none were present in the majority of patients. Only a handful were mutated more than 10% and over 30 genes were mutated in less than 5%. Understanding the prognostic value of this 'long tail' of recurrently mutated genes will require analysis of very large cohorts to identify enough patients with each mutation. Even then, these patients are likely to have different patterns of mutations in other genes which could confound their interpretation.

Another challenge to the integration of somatic mutations involves the clonal nature of MDS. Karyotype analyses have demonstrated that MDS can clonally evolve over time and that such evolution is associated with a poor prognosis.[44] But clonal evolution is largely missed in practice since standard cytogenetics has poor sensitivity to detect small subclones and most patients with MDS have normal metaphase karyotypes. Quantitative DNA sequencing methods are better equipped to detect low abundance mutations and can be used to describe the clonal architecture of MDS at the genetic level. Using these approaches, mutations can be assigned to either the dominant disease clone, representing the majority of tumor cells, or to a smaller disease subclone. Whether a mutation carries the same prognostic value when it is present in a dominant clone *versus* a subclone is not always clear. A typically favorable abnormality, like del(5q) for

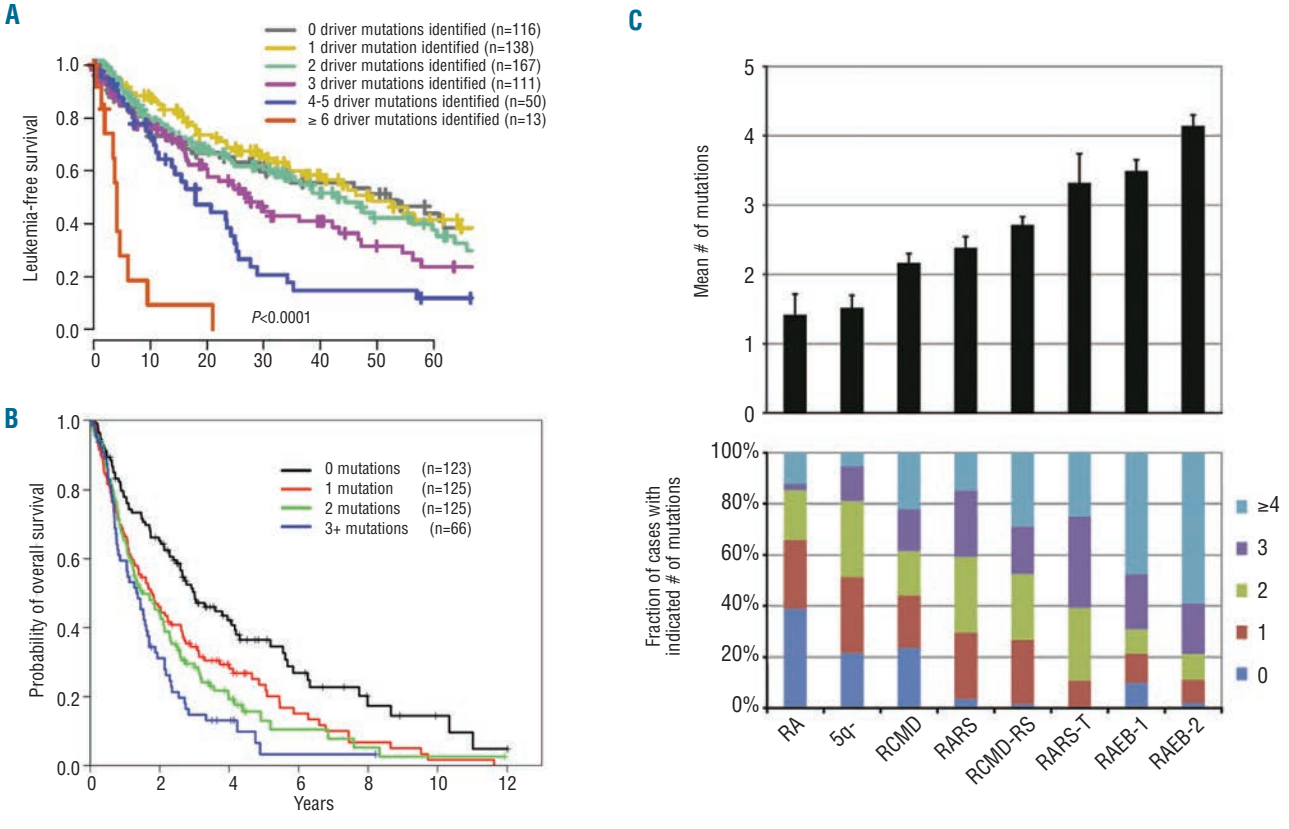

Figure 2. Somatic mutations are associated with disease risk and MDS subtype. (A) Kaplan-Meier curve from Papaemmanuil *et al.*[39] showing leukemia-free survival in 595 MDS patients stratified by the number of tumor mutations identified. (B) Similar figure from Bejar *et al.*[38] demonstrating the relationship between overall survival and mutation number in 439 MDS patients. (C) Data from Haferlach *et al.*[40] showing differences in mutation number across MDS subtypes. Reprinted with permission.

example, may not be associated with better disease risk if present only in a fraction of tumor cells. In contrast, gene mutations associated with poor outcomes appear to be equally adverse when present in subclones or the dominant clone.[39]

Mutation data can improve myelodysplastic syndrome prognostic models

Despite these challenges, genetic mutations can improve our ability to predict outcomes in MDS. For instance, in order to exist, subclones must have acquired a growth advantage over their parent clone. Subclones are often defined by the acquisition of additional driver mutations and may eventually manifest as more clinically advanced disease.[45,46] Current techniques can detect low abundance mutations long before the small subclone that contains them has a noticeable clinical impact. This could allow for earlier identification of risk in patients who have yet to experience the clinical consequences of adverse subclonal mutations. In their study of secondary AML, for example, Walter *et al*. demonstrated that the major clone present at the time of AML transformation could often be detected as a much smaller disease subclone months earlier while patients still had MDS.[45] This phenomenon is not limited to high-risk cases. Non-complex del(5q) abnormalities are considered favorable and predict deep responses to treatment with lenalidomide. However, highly adverse *TP53* mutations often co-exist in patients with del(5q), including those with del(5q) as their sole karyotype abnormality.[41,43] Isolated del(5q) patients with *TP53* mutations appear to have a poorer prognosis and an earlier relapse after lenalidomide treatment than expected, even in cases where the initial *TP53* mutant subclone is very small.[47] This finding justifies *TP53* screening of all patients prior to treatment with lenalidomide, as suggested by the ELN guidelines.[4]

Occult *NRAS* and *FLT3* mutations represent another example of how detecting subclonal mutations can refine the prediction of prognosis. *NRAS* and *FLT3* mutations are almost always late events in MDS progression, are typically subclonal, and predict transformation to AML.[48] When detected by conventional means, *NRAS* mutations may be present in 20-80% of tumor cells and are often associated with the high-risk features of increased blast proportion and thrombocytopenia. However, in lower risk MDS patients who lack these clinical features, even very low abundance of *NRAS* mutations, detectable only with highly sensitive techniques, are still associated with shorter overall survival.[49] The situation is similar with recently discovered mutations in the *SETBP1* gene that also appear to be late subclonal events associated with leukemic progression.[50-54]

Mutations in several of the more frequently mutated genes can carry prognostic value that is independent of the IPSS.[38,40] Bejar *et al*. demonstrated that MDS patients with one or more mutations of *TP53, RUNX1, ASXL1, EZH2,* or *ETV6* had an overall survival that was more like that of patients in the next highest IPSS risk group.[38] In particular, one-third of patients with 'lower risk' Intermediate-1 disease carried mutations that identified them as having a predicted overall survival resembling patients in the 'higher risk' Intermediate-2 group. Reanalysis of this cohort with regard to the IPSS-R shows a similar result (Figure 3A-C) that is largely validated in the supplement to Haferlach *et al*.[40] This may be of particular importance in those patients with IPSS-R Intermediate risk disease that, according to NCCN guidelines for MDS, could be treated in either the higher or lower risk pathways. In contrast, mutations of *SF3B1* may predict a more favorable prognosis, although there is conflicting evidence about their independent prognostic value.[40,55-57]

Mutations may have their greatest value in specific subsets of patients. For example, Bejar *et al*. examined MDS patients with complex karyotypes, about half of which carried a *TP53* mutation.[38] The complex karyotype is a high-risk component of nearly all prognostic scoring systems, but as shown in Figure 3D, patients with complex karyotypes who lacked *TP53* mutations had an overall survival that was comparable to that of patients with non-complex karyotypes. The adverse prognostic significance of the complex karyotype is almost entirely explained by its frequent association with *TP53* mutations. This may be partially captured by the IPSS-R where a distinction is made between patients with 3 cytogenetic abnormalities and those with 4 or more, a group that is more likely to have *TP53* mutations.[7,58,59] Similarly, Itzykson *et al*. crafted a prognostic model for CMML that combines clinical and genetic features, emphasizing the adverse prognostic impact of *ASXL1* mutations in this disease subtype.[19]

These examples demonstrate how tumor sequencing can add to existing prognostic models. Another approach would be to create an entirely new model that includes both molecular and clinical data. Haferlach *et al*. generated a prognostic model based solely on mutations in 14 recurrently mutated genes associated with differences in overall survival (Figure 3E).[40] Then they created an expanded model that incorporated an additional 6 clinical variables (Figure 3F). The combined model improved risk stratification, but only slightly, demonstrating how much prognostic overlap there is between mutational data and clinical phenotypes. These models are complex and unlikely to be adopted clinically without further refinement and validation. However, they demonstrate how mutational data might be made more interpretable in practice. Other complex prognostic tests in oncology, like Oncotype DX, used in certain breast cancer patients, return a composite risk score based on the results of several combined assays. This simplifies its interpretation and has facilitated its clinical use.[60] As we learn to overcome the challenges of genetic testing in MDS, we may opt for a similar approach to improve the prediction of prognosis in our patients.

Summary and future directions

Systemic approaches to predicting disease outcomes for patients with MDS have become highly sophisticated and are an integral part of care. The original IPSS helped standardize estimates of disease risk between patients in clinical trials and defined how physicians might tailor their treatment options. Additional models were created to refine the prediction of prognosis and address the perceived shortcomings of the IPSS. The IPSS-R is rapidly becoming the standard tool for MDS risk assessment and has been validated in a variety of clinical contexts that widen its applicability.

Additional biomarkers that can improve upon the IPSS have been discovered. Of these, recurrently mutated genes are most likely to become part of the routine care of patients with MDS. Genetic testing is increasingly available and clinical applications beyond prognosis are being

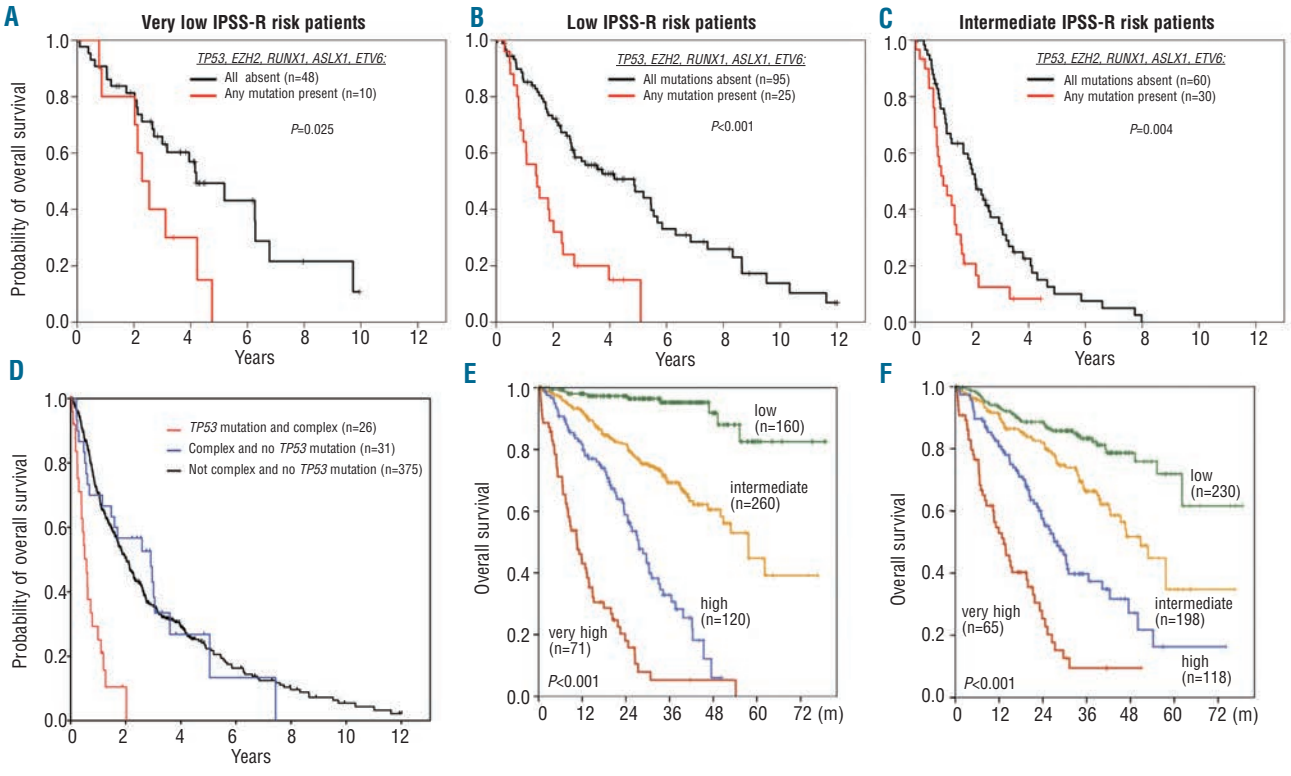

Figure 3. Combining somatic mutations with known risk factors and prognostic models. (A-C) Data from Bejar *et al.*[38] is used to compare overall survival in patients with one or more prognostically adverse mutations (in *TP53*, *EZH2*, *RUNX1*, *ASXL1*, or *ETV6*) to unmutated patients within each of the IPSS-R 'lower' risk groups. Mutations identify added disease risk in each of the categories. (D) Overall survival of patients with complex disease karyotypes is strongly stratified by *TP53* mutation status. Patients with both a complex karyotype and *TP53* mutation have a very short overall survival whereas complex karyotype patients without a *TP53* mutation have a survival that is comparable to that of MDS patients with non-complex karyotypes. (E) Overall survival in 611 MDS patients examined by Haferlach *et al.*[40] and stratified according to a mutation-only prognostic model considering the weighted contribution of mutations in 14 genes. (F) Overall survival in the same 611 patients risk stratified by a prognostic model that combines both clinical features and the mutation status of 14 genes. Reprinted with permission.

developed. For example, somatic mutations may be used as markers of clonal hematopoiesis to aid in the diagnosis of MDS, they may help molecularly define MDS subtypes, and they could be used to monitor for disease evolution or relapse. Eventually, mutation profiles may help predict response to specific therapies. Together, these indications will further drive demand for molecular genetic tests in the clinical setting. The International Working Group for Prognosis in MDS is developing methods to integrate genetic and clinical biomarkers in order to better predict the prognosis of patients with MDS. In the meantime, mutations in several genes can add to existing risk models and refine the prediction of prognosis. This may be particularly useful for identifying patients in the Intermediate IPSS-R risk group with high-risk genetic features.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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