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MINI REVIEW

Myelodysplastic Neoplasms: The Impact of Clonality on Inflammatory-Degenerative Diseases of the Elderly

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The diagnostic approach to patients with cytopenia has become highly challenging due to the heterogenic presentation of clonal hematopoietic stem cell disorders and accompanying degenerative disorders in the generally elderly population. A holistic approach with extensive clinical experience is required to recognize the potential interactions between the clonal condition and inflammatory-degenerative comorbidities in the elderly. This narrative review highlights the diagnostic challenges in the classification and risk stratification of patients with clonal hematopoiesis and myelodysplastic neoplasms, dysregulation of immune hemostasis and its impact on degenerative-inflammatory comorbidities of the elderly from the perspective of an experienced clinician.

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Introduction

Myelodysplastic neoplasms (MDS) are a heterogeneous collection of hematologic hematopoietic stem cell malignancies that ultimately result in cytopenia, dysplasia, ineffective hematopoiesis and eventually, acute myeloid leukemia (AML). Dysregulation of inflammatory and immune hemostasis

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has been increasingly recognized as an important co-factor in the development and progression of clonal hematopoiesis towards overt myeloid malignancy, such as MDS.[1]

In Switzerland, >300 new MDS cases are reported each year.[2] The risk of progression to AML among patients with high-risk MDS is high (~40%).[3] MDS is an emerging disease in the elderly (the majority of patients are aged >70 years),[4] and due to an aging population in developing countries and the recent molecular advances in detecting clonality, the case-frequency of MDS is expected to increase over time with a high impact on health resources.[5,6] As MDS is mainly a disease of the elderly, comorbidities play an important role in the presentation and symptom burden of affected patients. This explains the high heterogeneity of clinical manifestations and requires a proper understanding of the impact of clonally affected immune cells on the frequently inflammatory-driven degenerative conditions of the elderly population (inflammaging).[7]

While recent advances in targeted precision therapies (e.g., large-scale next generation sequencing [NGS]) have brought more clarity to the genetic landscape underpinning MDS,[8] management plans for MDS step behind and require further development in the understanding of the disease and its interaction with comorbidities. Low-risk patients do not benefit from immediate disease-modifying therapies and are mainly treated symptomatically with transfusions and growth factors.[9,10] However, our growing understanding of immune dysregulation in MDS pathogenesis (e.g., abnormal activation of innate immune pathways and associated inflammation, aberrant cellular immune responses) provides the foundation for future developments in reducing or even reverting clonal progression to higher-risk MDS or leukemia.[6] This may not only reduce the leukemic risk but, more importantly, also revert some of the associated inflammatory-degenerative contributions to comorbid cardiovascular, pulmonary, metabolic, neurological and musculoskeletal conditions in elderly patients. The combination of genomic and immunogenic profiling is on the rise and will substantially influence the development of new classifications and prognostic models as well as treatments of MDS patients. These developments may be considered a modest steps towards rejuvenation of the hematopoietic system with the aim to reduce the clonal burden of the disease.[6,11]

Myelodysplastic neoplasms

Peripheral cytopenia (e.g., anemia, neutropenia and thrombocytopenia) coupled with morphological dysplasia are laboratory hallmarks of MDS.[12,13] However, since the advent of NGS, the detection of clonality in individuals with "quasi-normal" blood counts has resulted in the identification of a substantial number of mainly elderly patients with clonal hematopoiesis.

These mutations are frequently affecting genes of proteins involved in the epigenetic machinery (*TET2, DNMT3A, ASXL1*). MDS is characterized by usually more than one mutation in an array of >40 genes, with mutations affecting the spliceosome (i.e., *SF3B1, SRSF2, U2AF1, ZRSR2*) or *TP53*, which carry the highest correlation with morphological dysplasia. However, none of these gene mutations are specific to MDS, and clonal evolution over years results in complex gene-gene interactions[14] and the involvement of genes that are more prone to a proliferative phenotype (i.e., *JAK2, KRAS*) or even secondary leukemic transformation (i.e., *NPM1, FLT3*) (**Figure 1**).[15-25] Cytogenetic alterations defining MDS-related AML have been identified, and more recently also genetic MDS features (somatic mutation patterns) have been defined in the novel International Consensus Classification (ICC)[26] and the World Health Organization (WHO) classification.[27]

Disease-modifying treatment is only recommended for patients with high-risk features, including severe cytopenia (or cytosis), increased blast counts, fibrosis and, more recently, high-risk genetic features for leukemic transformation (i.e., number of genes affected, burden of clonality, AML transformation genes affected). These treatments include palliative epigenetic therapy with hypomethylating agents for the elderly, while for the (minority of) younger and fit patients, the only curative treatment remains allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Asymptomatic lower-risk patients are currently not treated at all and those with symptomatic anemia may require transfusions, use of growth factors (erythropoietin-stimulating factors) or, more recently, maturating agents (i.e., luspatercept). Early disease-modifying treatment in lower-risk MDS patients currently has no impact on leukemia-free survival (LFS) or overall survival (OS). Therefore, care for lower-risk patients focuses generally on the quality of life with ameliorating symptoms of cytopenia and delaying transformation to higher-risk features and AML.[28,29] Therapy is prioritized for patients requiring frequent blood transfusions.[9] The prognosis in LFS and OS are determined by a number of different parameters, including the degree of cytopenia, the proportion of excess blasts in peripheral blood or bone marrow (BM) as well as cytogenetic and, more recently, genetic features.[30]

Diagnostic criteria

The diagnosis of MDS can be made using peripheral blood counts, a peripheral blood smear, aspiration and biopsy of the BM, cytogenetic analysis and, more recently, NGS.[32] Pre-requisite diagnostic criteria for MDS include (note that both criteria must be fulfilled): (1) cytopenia that has been observed for at least four months or longer and (2) the elimination of other potential causes of dysplasia and/or cytopenia(s).[33]

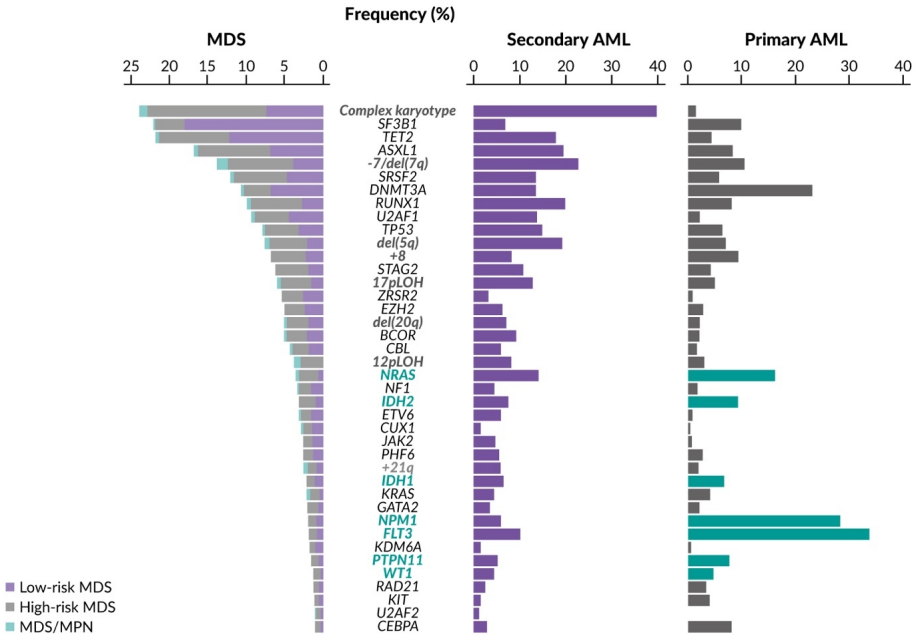

Figure 1. Driver mutations in myelodysplastic neoplasms (MDS) and differences between primary and secondary acute myeloid leukemia (AML).

MPN, myeloproliferative neoplasms. Adapted from Ogawa et al. 2019.[31]

Valent et al. (2019) noted that to confirm diagnosis of MDS, at least one of the following criteria is required: (1) signs of dysplasia in ≥10% of all cells in one or more major blood cell lines (e.g., erythroid, neutrophilic and megakaryocytic) or an elevation of ring sideroblasts to ≥15% (or to ≥5% when an *SF3B1* mutation is found), (2) a myeloblast excess of 5–19% in BM aspirate smears or 2–19% circulating myeloblasts and (3) detection of an MDS-associated chromosome abnormality (e.g., 5q–, –7, or a complex karyotype).[33] More recently, also genetic features have been characterized and are increasingly accepted as MDS-defining alterations. However, the current ICC and WHO classifications remain inconsistent in the view of the author, as genes defining MDS-related AML (AML-MR) (mostly spliceosome-genes) do not define MDS in the context of clonal cytopenia, with the exception of *SF3B1* mutations at a variant allele frequency (VAF) of >10% or *TP53* mutations. Subtypes of MDS can be defined using the following criteria: the number of immature cells in the BM, the amount of ringed sideroblasts (such as iron-loaded blood cell precursors) or *SF3B1* mutations and the presence of cytogenetic aberrations (including the elimination of the long arm of a chromosome) and mutations in two specific genes (*TP53* and *SF3B1*).[13] For all other mutations, the diagnostic impact remains unclear, however preclinical data points towards a relevant impact in early detection of MDS cases.[34]

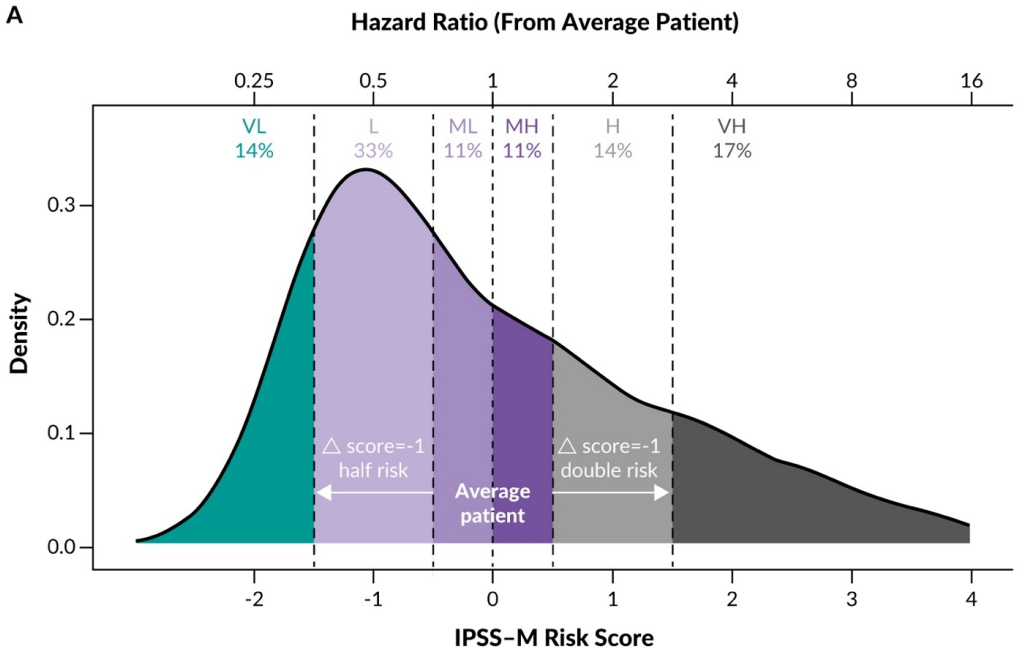

Figure 2. Myelodysplastic neoplasm (MDS) risk stratification by the International Prognostic Scoring System-Molecular (IPSS-M) score.

H, high; L, low; MH, moderate-high; ML, moderate-low; VH, very high; VL, very low. Adapted from Bernard et al. 2022.[37]

Prognostic instruments

The most common and recommended prognostic instrument for MDS is the revised version of the International Prognostic Scoring System (IPSS-R) with five risk groups (LR-MDS being subdivided into IPSS-R very low, low and intermediate up to 3.5 points). These risk groups are associated with different likelihoods of progression to AML as well as overall survival outcomes.[32] While the IPSS-R is a good tool for estimating risk, it is lacking in predicting response to therapy (as it was based on patients with untreated disease); therefore, the addition of other elements (e.g., genomic and immunogenic data) may lead to better stratification.[6] An example of this can be seen with del(5q), which predicts a better response to lenalidomide in low-risk patients.[9,35] In response to this need, a newly developed risk stratification instrument called the IPSS-molecular (M) has been developed for MDS that incorporates molecular data. This new score uses six risk categories and has shown improved outcome prediction for both LFS and OS (**Figure 2**).[36] With the IPSS-M, 48.2% of the patients were re-stratified, of which 16.9% were downgraded and 31.3% were upgraded; based on the results of this cohort, the treatment of 22.2% of patients would be affected (17.4% would be eligible for treatment intensification and 4.8% for treatment reduction).[36] Patient with IPSS-R intermediate profit most form using the refined IPSS-M instrument.

How precision medicine can improve the diagnosis of MDS

Advances in NGS have allowed for greater knowledge of an individual patient's genomic profile and open the door for further personalization of treatment. In MDS, recurrent somatic mutation genes can be split into five functional categories: RNA splicing, epigenetic regulation (DNA methylation, histone modification), DNA transcription, signal transduction and chromatid cohesion (**Figure 3**).[8,38] However, while the presence of some of these somatic mutations may prove helpful in categorizing risk, their utility in MDS diagnosis is limited as less than 50% of patients with *de novo* MDS will have detectable karyotype abnormalities and the role (except for *TP53* and *SF3B1* mutations) remains unclear.[39] As mentioned previously, the IPSS-M is a new risk assessment model harnessing the power of mutational patterns to improve patient stratification towards observation or treatment, consensus on their diagnostic impact needs to be refined in the oncoming years.[36]

In Europe, treatment options for MDS are limited, particularly for low-risk MDS and even more so in Switzerland. The European Medicines Agency (EMA) has approved lenalidomide, azacytidine, erythropoiesis-stimulating agents (ESAs) and luspatercept in the last two decades, with the latter not approved in Switzerland. Many other compounds are under investigation.[9,40] This limited pool of agents can hamper the use of NGS in patients who may benefit from different treatment approaches.

Currently, some specific mutations have been suggested to predict for shorter OS after allo-HSCT (e.g., *TP53*, *TET2*, *DNMT3A*, *RUNX1* and *ASXL1)*,[41] however, *TP53* is the only independent predictor of shorter OS across cohorts.[42] Some potential uses for NGS include the detection of residual disease and predicting relapse following transplant.[43] It should be noted that the use of NGS may be restricted due to: (1) the time taken to receive data outputs (i.e., one to three weeks), which may not be ideal in patients with quickly evolving disease, (2) overall cost of the gene panels, although this is likely to decrease with time and (3) a lack of standardization across NGS gene panels and data interpretation, which can affect the identification of genetic signatures for treatment.[41] Despite these caveats, it is desirable to perform NGS in the majority of MDS patients. Since the *SF3B1* and *TP53* mutations are listed as an independent subtypes in the revised WHO classification,[44] its evaluation is recommended in all cases. NGS may help confirm clonal disease in patients with signs of cytopenia and only mild dysplasia in BM aspirates.[45] The number of mutations as well as higher VAFs identified by NGS may enable distinction between the diagnosis of MDS and clonal hematopoiesis of indeterminate potential (CHIP).[46] The identification of AML-defining *CEBPa*, *FLT3* and *NPM1* mutations[47] may also be important in patients with higher blast counts (close to the threshold of 20%). With its

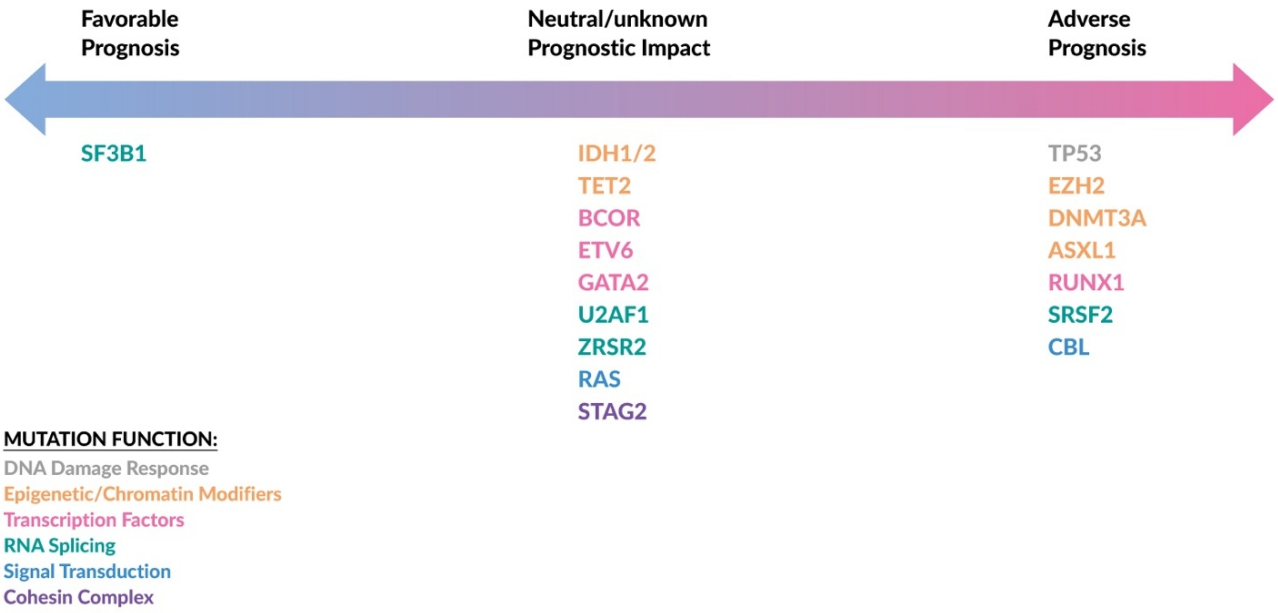

Figure 3. Prognostic impact of mutations in myelodysplastic neoplasms (MDS).

Adapted from Cook et al. 2022.[38]

diagnostic and prognostic relevance and the identification of novel molecular markers, the use of NGS in patients with MDS is likely to revolutionize the management of MDS in the future.

MDS management plan

The treatment of MDS is adapted to disease- and patient-based risk, with different goals (**Figure 4**). In patients with low-risk disease, the primary goal of therapy is to reduce cytopenia and improve the quality of life, due in part to the mild and asymptomatic nature of cytopenia, as well as the risk posed by active therapy to patients who may already have a short life expectancy due to other comorbidities.[9,32] Although some low-risk patients with a "higher-risk" profile, due to the presence of unfavorable genomic mutations (e.g., *ASXL1, RUNX1, ETV6 and TP53*), may benefit from close meshed surveillance.[9] Prolonging OS is the primary goal in patients with high-risk disease, with the potential for disease cure if patients are eligible for allo-HSCT.[32]

With respect to supportive care, the majority of patients require regular blood transfusions. This may result in the accumulation of excessive amounts of iron (250 mg per red blood cell unit), which in turn will require chelating therapy. In low-risk patients, ESAs are the first-line therapy in those who are likely to respond (e.g., <200 IU/L endogenous erythropoietin level and a transfusion burden <4 U, within an 8-week period).[9,32]

In low-risk patients, treatment with lenalidomide may be an option for individuals with del(5q) and excessive erythropoietin levels. Immunosuppressive agents like anti-thymocyte globulin/cyclosporine A with

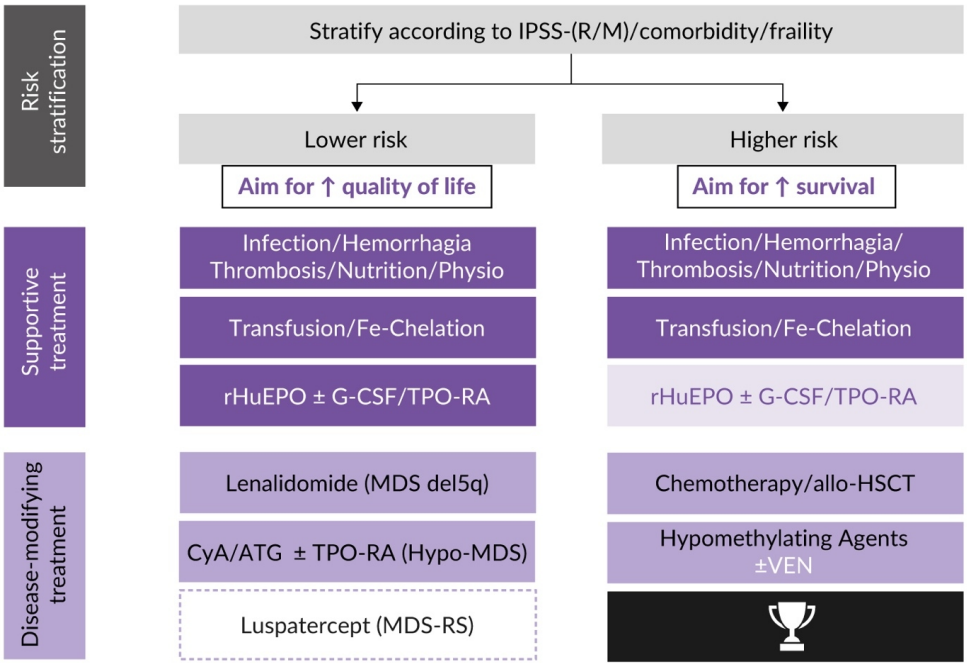

Figure 4. Management of myelodysplastic neoplasms (MDS) according to risk status.

allo-HSCT, allogeneic hematopoietic stem cell transplant; ATG, anti-thymocyte globulin; CyA, cyclosporine A; FE, iron; G-CSF, granulocyte colony-stimulating factor; hypo, hypoplastic; IPSS-(R/M), International Prognostic Scoring System-(Revised/Molecular); MDS-RS, myelodysplastic neoplasms with ring sideroblasts; rHuEPO, recombinant human erythropoietin; TPO-RA, thrombopoietin receptor agonists; VEN, venetoclax.

and without thrombopoietin-receptor agonists (TPO-RA) are recommended in patients with hypoplastic MDS and normal karyotype failing the first-line therapy with growth factors.[32]

In high-risk patients, allo-HSCT should only be considered in individuals with intermediate-2 or high risk, while hypomethylating agents (azacytidine, decitabine) are the standard of care for those patients requiring intensive treatment approaches.[32] Due to the potential treatment-related complications associated with allo-HSCT, the appropriate selection of patients is crucial.[48]

Origin of immune dysregulation in MDS

Pre-MDS clonal expansion in the elderly: CHIP and CCUS

Clonal expansion of a set of blood cells from a single hematopoietic stem cell progenitor is termed clonal hematopoiesis (CH).[49] Originally, a defining characteristic of hematologic cancers, CH has now also been associated with aging.[49,50] The reason why some patients with CH progress to overt hematological neoplasms and why others do not is currently of high academic interest. These investigations may lay the foundation for potential "cure" of patients with MDS and AML by early intervention in those individuals with high risk of progression. In the case of MDS and other blood disorders, some notable forms of clonal expansion are CHIP and clonal cytopenia

of undetermined significance (CCUS) (**Figure 5**).[5,49,51] Differentiating between diagnoses of CHIP, CCUS, idiopathic cytopenia of unknown significance (ICUS) and idiopathic dysplasia of unknown significance (IDUS) may be important for guiding treatment decisions, assessing prognosis and effectively stratifying risk. Each condition carries distinct implications for patient management, ranging from uncertainty regarding the significance of genetic mutations to heightened risk of hematological malignancies and cardiovascular diseases. A clear diagnosis also facilitates inclusion in clinical trials, enabling the development of targeted interventions.

CHIP is a condition that is characterized by the presence of somatic gene mutations in blood cells, most commonly in older people, in the absence of blood cell count abnormalities or obvious indicators of a myeloid neoplasm.[5, 51] *DNMT3A*, *TET2*, *ASXL1* and *JAK2* are examples of mutated genes in patients with CHIP with an VAF <10%.[32,51-53] These conditions can be an early indicator of more serious blood disorders, such as MDS, myeloproliferative neoplasms (MPN) or AML; however, it is important to note that the risk of CHIP developing into these more severe phases may vary, as stated before.[54]

In contrast, CCUS concerns patients with unexplained cytopenia, characterized by lower-than-normal blood cell counts, in conjunction with evidence of CH at higher VAFs. This condition has been linked to somatic mutations in hematopoietic stem cells, raising the risk of myeloid malignancies.[34] Following diagnosis, patients with CCUS require closer monitoring to assess disease stability[5] and the risk of progression to MDS or another hematologic malignancy.[28,33]

Patients with ICUS represent another diagnostic class in relation to MDS. CCUS can be differentiated from ICUS, which lacks any relevant somatic mutation (VAF <2%) and can be caused by a variety of comorbid conditions.[55] When compared to ICUS or CHIP, CCUS is associated with a higher risk of developing MDS/AML, especially in younger individuals or children.[56] The presence of ICUS or CCUS highlights some of the complexities involved in detecting and managing clonality in blood cells, particularly in older populations that are affected by many other disorders associated with cytopenia.[5] However, in those patients it remains still important to identify “clonality” as more recent studies clearly show that clonal affected immune cells impact on inflammatory-degenerative disorders of the elderly, such as cardiovascular, metabolic, pulmonary and neurological conditions. As yet, we do not sufficiently understand how to tackle this vicious interaction, and we are currently facing the convergence of rheumatology and hematology in the field of hyperinflammatory conditions associated with clonal hematopoiesis and hematological neoplasms. As a result, continuous medical examination by experienced physicians is required to evaluate the interaction of clonally driven hyperinflammation with

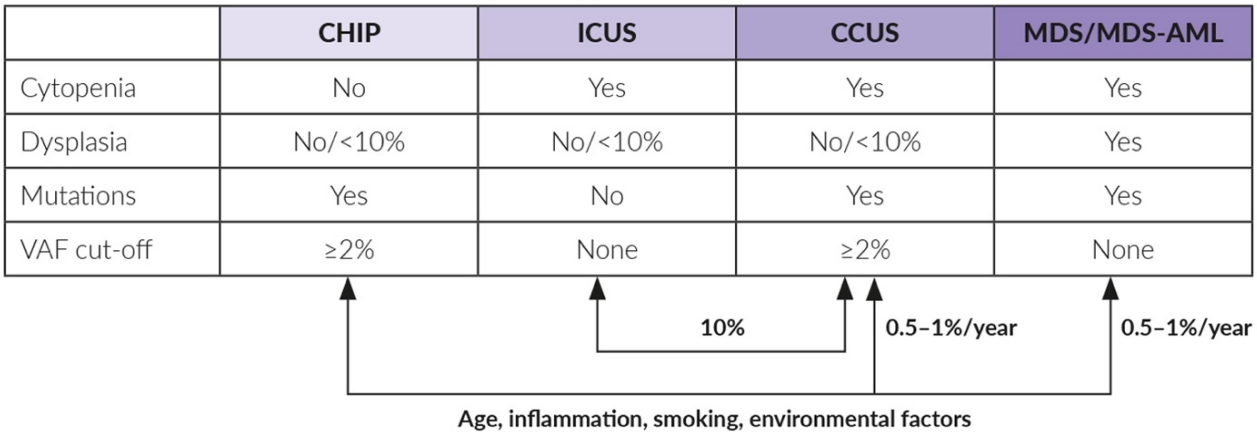

Figure 5. Myelodysplastic neoplasm (MDS)-overlapping disorders.

AML, acute myeloid leukemia; CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; ICUS, idiopathic cytopenia of unknown significance; VAF, variant allele frequency. Adapted from Falini et al. 2023.[58]

comorbidities and the risk of progression to more severe illnesses such as MDS and AML as well as the impact on complications from other comorbidities (infectious risk, myocardial infarction, thrombo-embolism, aggravation of COPD and hyperinflammatory conditions).[57] This field is still in its infancy and will substantially change the way we will manage MDS patients in the future.

Linking the inflammasome with the pathophysiology of MDS

Inflammation is an underlying factor that has long been associated with tumor progression.[59] In MDS, key drivers of tumorigenesis are related to aberrant innate immune activation and proinflammatory signaling interacting within the malignant clone and the BM microenvironment.[60] Aging, chronic infection and autoimmune/autoinflammatory disease are all factors that promote chronic inflammation or "smoldering inflammation",[61] and therefore may all promote clonal evolution to MDS (**Figure 6**). Toll-like receptor (TLR) signaling, an important part of the innate immune system, has been found to be upregulated in MDS, with overexpression of TLRs observed in hematopoietic stem and progenitor cells of patients, compared with age-matched controls.[62] Sustained activation of TLRs may cause "myeloid bias" of hematopoietic stem cells and multipotent progenitors, promoting the accumulation of somatic mutations conferring clonal advantage and/or differentiation defects toward the myeloid lineage.[63]

In MDS, S100A9-mediated nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome activation is driven by elevated levels of proinflammatory cytokines, reactive oxygen species (ROS)/reactive nitrogen species (RNS) and damage-associated molecular patterns (DAMPs) leading to an inflammatory, lytic form of cell death called pyroptosis which affects the hematopoietic stem and precursor cells

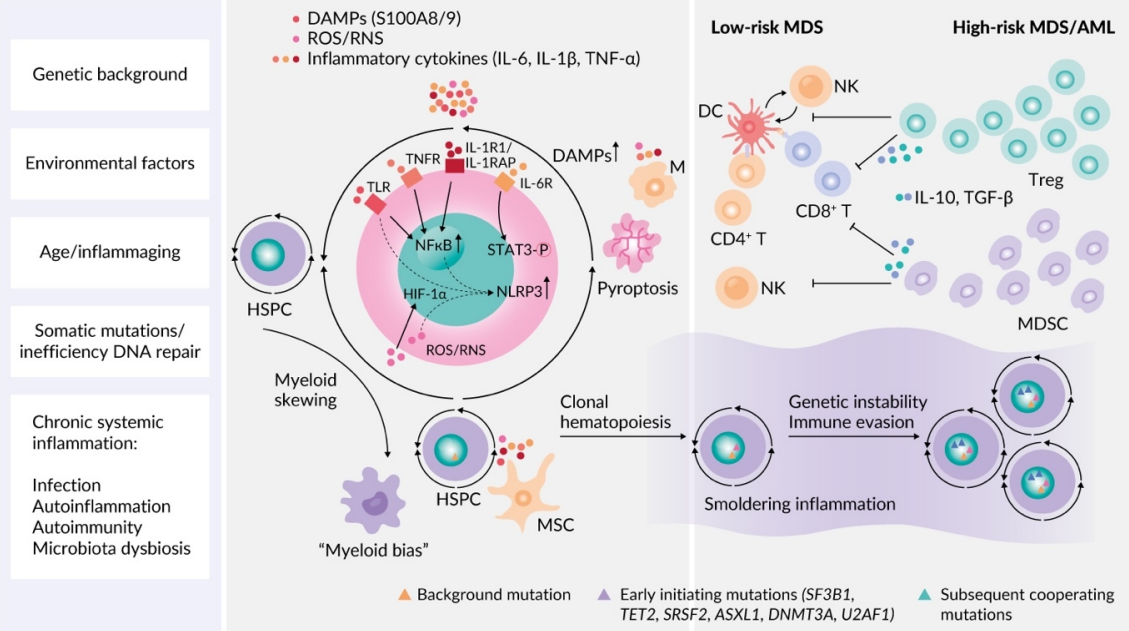

Figure 6. Immune-mediated pathophysiology of myelodysplastic neoplasms (MDS).

AML, acute myeloid leukemia; ASXL1, additional sex combs-like 1, transcriptional regulator; DC, dendritic cell; DNMT3A, DNA methyltransferase 3 alpha; HIF-1a, hypoxia-inducible factor 1, alpha subunit; HSPC, hematopoietic stem and precursor cells; IL, interleukin; IL-1R1, interleukin-1 receptor, type 1; IL-1RAP, interleukin-1 receptor accessory protein; M, macrophage; MDSC, myeloid-derived suppressor cells; MSC, mesenchymal stromal cell; NF-κB, nuclear factor kappa B; NK, natural killer cell; NLRP3, nucleotide-binding domain and leucine-rich repeat pattern recognition receptor (NLR) family, pyrin domain-containing protein 3; SF3B1, RNA splicing factor 3B, subunit 1; SRSF2, serine/arginine-rich splicing factor 2; STAT3-P, signal transducer and activator of transcription 3, phosphorylated; TET2, tet methylcytosine dioxygenase 2; TGF-β, transforming growth factor-beta; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; Treg, regulatory T cells; U2AF1, U2 small nuclear RNA auxiliary factor 1. Adapted from Winter et al. 2020.[6]

(HSPCs).[6,64] This leads to the further release of DAMPS and expands BM myeloid-derived suppressor cells, further activating the inflammasome.[60] The NLRP3 inflammasome complex has been proposed as a disease-specific biomarker for MDS and suggested to be responsible for hallmark features of MDS (e.g. macrocytosis, β-catenin–instructed proliferation and ineffective hematopoiesis).[60,65] While low-risk MDS is characterized by immune hyperactivation and increased apoptosis, the opposite is true for patients with high-risk MDS.[6,66] In this case, the expansion of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) leads to the suppression of CD8+ anti-tumor signaling,[67] followed by immune evasion by cancer cells.[6, 68]

Establishing a link between MDS and other inflammatory degenerative disorders

CHIP or age-related CH caused by somatic mutations in HSPCs can result in hematologic disorders through clonal expansion.[46] As many of these mutations impact immune effector cells (e.g., monocytes, granulocytes and lymphocytes), they may in turn lead to the development of immunological

disorders, in particular illnesses associated with deregulated innate and adaptive immunity.[69] In patients with CHIP, the most common mutations involve loss of function in *DNMT3A* and *TET2* genes, and recent studies have linked both genes to the innate immune system.[69] Mutations in *JAK2*, which commonly occur in MPN, have also been shown to increase activation of granulocytes and T cells, enhancing inflammation in macrophages.[70-72]

CHIP has been associated with increased levels of congestive heart failure and ischemic stroke with a hazard ratio of approximately 2. *JAK2*-mutated CHIP has been shown to be associated with an increased risk of thrombosis, a link shared by other CHIP-related genes.[73] *DNMT3A*, *TET2* and *JAK2* have also been linked to an increased risk of heart failure in mouse models. Furthermore, CHIP has been associated with the development of type II diabetes; however, the causal relationship between these two disorders remains unclear.[50] Ongoing studies are evaluating whether non-cardiovascular inflammatory disorders such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis or Alzheimer's/Parkinson's disease may harbor a connection with CHIP.[69] In the case of COPD, there are some studies supporting a link,[74,75] however, this finding is confounded by the fact that smoking is a risk factor associated with both. Regarding rheumatoid arthritis, there is little evidence of a link; this is likely unsurprising, as T cells and B cells (which are thought to drive autoimmune disorders) rarely contain CHIP-associated mutations.[69] In the case of Alzheimer's and Parkinson's disease, research is still needed to determine whether a relationship exists with CHIP, although, one study has shown the presence of *DNMT3A* and *TET2* mutations in whole-brain DNA of elderly patients.[76] Concerning specific treatments of inflammatory conditions in MDS, most may respond to steroids but consensus on which compound by be beneficial remains unclear and has to be established on individual level.

Looking forward: Systems immunology

Available evidence clearly links the "immunome" as an important contributor to the development and progression of MDS. Stratifying patients with MDS by immunogenic "risk factors" may be attractive for advancement in the field. Evaluating the immune state or "fitness" of a patient requires a broad, holistic approach; it currently lacks wide consensus, and the impact of altering the immune system remains unclear. However, it needs to be emphasized that hypoplastic MDS responds very well to T cell-directed therapy with cyclosporine, and the curative part of allo-HSCT is conveyed by the immunogenic eradication of leukemic cells by a donor-derived immune cell-driven graft versus leukemia (GvL) effect. A multi-omics approach, taking clinical data into consideration, is required to provide robust and predictive immune signatures and map the interaction between disease-associated inflammation and potentially host-beneficial cellular immune responses.[6] The use of immunologic markers and an "immunoscore" to assess "immune

fitness" are some of the potentially useful concepts that need further developments.[6] Examples of success for mutational profiling in MDS using comprehensive myeloid NGS panels include: (1) multiparameter flow cytometry[6] which can monitor immune-modifying agents or minimal residual disease in high-risk MDS/AML and (2) cytometry by time of flight (CyTOF)[77] which has been shown to provide high resolution of the single-cell proteome, with predictive analysis of immune response to therapeutics, and which has been successfully used to perform immunophenotypic analysis and characterization of immune signatures in MDS cell populations.[6] Immunoscores have been successfully developed and implemented in solid tumors as prognostic tools,[78] and despite the differences in hematologic cancers, this provides a basis for pursuing a holistic multi-omics approach in MDS.

How to defeat clonal evolution?

The ultimate goal and "holy grail" in the treatment of MDS and AML would be the elimination of the source of clonal population upon detection of "higher-risk" CHIP or CCUS and the restoration of normal, polyclonal hematopoiesis. The noxious effects of CHIP/CCUS can be particularly highlighted in patients who require chemotherapy or radiotherapy for a non-myeloid neoplasm. Patients with CHIP/CCUS exposed to radiation or chemotherapy showed an increased risk of treatment-related MDS/AML (>25%).[49] Indicators for insufficient hematopoietic reserve are worsening of cytopenia following cytoreduction and marrow failure. Clonal evolution has also been shown to be a relevant issue in lower-risk del(5q) patients treated with lenalidomide, where the highly malignant *TP53*-clonal populations are clonally selected and associated with therapy resistance.[79] The currently limited pool of approved cytotoxic agents for patients with MDS also limits therapy choices, and even if remission occurs, due to the low-level persistence of mutant HSPCs, a cure can only be reached *via* an allo-HSCT.[80] Trials are ongoing to investigate earlier treatment regimens that reduce or revert the progression of CHIP/CCUS to MDS/AML.[49]

How do I diagnose/treat MDS patients with autoinflammatory and autoimmune manifestations

It is important, first of all, to be aware of the association of a variety of autoimmune and autoinflammatory manifestations with MDS or clonal hematopoiesis. In a recent study, we identified about 30% of MDS patients with a broad variety of immune dysregulation.[81] The occurrence in elderly individuals, atypical manifestation, immediate response to steroids and relapse on tapering are common hallmarks of MDS-associated immune dysregulation. The affected organs, the response to steroid-sparing treatments and the course of the conditions are highly variable and must be managed in cooperation with experienced rheumatologists.

Future perspectives and conclusions

MDS are complex and heterogeneous diseases. A growing body of knowledge shows that the correction of immune dysregulation may be beneficial as an early intervention to reduce clonal progression as well as ameliorate inflammatory-degenerative conditions of the elderly. As such, increasing our understanding of the interaction between the inflammasome and immunome may substantially change our current treatment paradigms in MDS. Improved diagnostics and early intervention have helped to identify clonality in elderly patients, and now we are embarking on our way to use these understanding in developing treatments that may avoid clonal progression. Ultimately, the increase of our knowledge coupled with clinical trials designed at early states of the disease will eventually reduce the development of more severe conditions that are difficult to eradicate in the elderly population.

Conflict of interest

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Author contributions

The author created and approved the final manuscript.

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