Clinical management of myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes

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ABSTRACT

The myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) are a unique group of hematologic malignancies characterized by concomitant myelodysplastic and myeloproliferative features. According to the 2008 WHO classification, the category includes atypical chronic myeloid leukemia (aCML), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), MDS/MPN-unclassifiable (MDS/MPN-U), and the provisional entity refractory anemia with ring sideroblasts and thrombocytosis (RARS-T). Although diagnosis currently remains based on clinicopathologic features, the incorporation of next-generation platforms has allowed for the recent molecular characterization of these diseases which has revealed unique and complex mutational profiles that support their distinct biology and is anticipated to soon play an integral role in diagnosis, prognostication, and treatment. Future goals of research should include the development of disease-modifying therapies, and further genetic understanding of the category will likely form the foundation of these efforts.

KEYWORDS

Myelodysplastic syndromes; myeloproliferative neoplasms; next-generation sequencing; CMML; aCML; JMML; MDS/MPN-U

Introduction

The myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) are a unique group of myeloid malignancies characterized by a paradoxical phenotypic presentation hallmarked by both myelodysplastic and myeloproliferative features. MDS-like features include cytopenias and dysplasia of various cell lines while MPN-like features can include constitutional symptoms (e.g. night sweats and/or weight loss), elevated blood counts as well as extramedullary infiltration. As designated by the 2008 World Health Organization (WHO) classification, the MDS/MPN group is comprised of chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML), and MDS/MPN unclassifiable (MDS/MPN-U)1,2. An additional provisional category is refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)1,2. Diagnosis and classification remain clinicopathologic, based on laboratory, morphological, and clinical parameters2. In general, the respective disorders are identified by the predominant myeloid subset present in the peripheral blood, such as the expansion of peripheral blood monocytes in CMML and JMML, and dysplastic granulocytes in aCML. RARS-T is demarcated by thrombocytosis while MDS/MPN-U is not associated with a specific myeloid subset, but is instead identified by the presence of overlapping myeloproliferative and myelodysplastic features at presentation and not meeting criteria for other subtypes3.

The underlying pathogenesis responsible for this group of neoplasms remains unclear as does the molecular convergence point that biologically defines the MDS/MPN category. The characteristic bone marrow phenotype involves increased cell death resulting in dysplasia and cytopenias alongside concurrent myeloid subset skewing and proliferation4. Although no molecular markers have been found to be entirely unique to disorders in the MDS/MPN category5, advances in the molecular characterization of these disorders and annotation of recurrent genetic mutations have furthered our understanding in the field (Table 1).

Specifically, these analyses have revealed substantial heterogeneity and complexity of molecular defects among the MDS/MPN group and elucidated several pathways likely involved in disease pathogenesis6-9.

Cytogenetic testing and high-resolution single polymorphism genotyping arrays (SNP-A) have detected chromosomal abnormalities in a large proportion of
MDS/MPN patients, most commonly aneuploidies (+8, +9, -7) and partial deletions (7q-, 13q-, 20q-) with a minority exhibiting reciprocal translocations involving tyrosine kinase fusion genes\textsuperscript{10,11}. In addition, large regions of uniparental disomy (UPD) have been identified in around one-third of MDS/MPNs through SNP-A analysis, which are associated with mutations involving gain of function in oncogenes or loss of function in tumor suppressor genes\textsuperscript{5,10}. In a mixed cohort of patients with myeloid malignancies, SNP-A detected UPD in 48% of CMML and 38% of MDS/MPN-U patients\textsuperscript{12}. Deregulation of myelopoiesis-associated microRNA/miR has also been demonstrated in cases of aCML and CMML, which exhibited down-regulation of miR-10a and overexpression of miR-424, respectively\textsuperscript{13}.

| Table 1 | Frequencies of recurrent genetic mutations in MDS/MPNs |
| Cellular pathway | Gene | Frequency (%) |
| | | CMML | JMLL | aCML | MDS/MPN-U | RARS-T |
| Signaling | K/N RAS | 19 | 39 | 35 | 10 |
| | JAK2 | 8 | 0 | 4-8 | 57 |
| | JAK3 | N/A | 12 | |
| | MPL | |
| | CBL | 10 | 15 | 8 | >10 |
| | KIT | >5 | >5 | 3 |
| | FLT3 | 1-3 | 5 | 3 |
| | CSF3R | 0 | 0 | <10 | 0 |
| | SETBP1 | 6-15 | 8 | 48 | 10 |
| | NOTCH2 | Rare |
| | PTPN11 | <1 | 44 | Rare |
| | NF1 | Rare | 13 | Rare |
| | CALR | 0 | 0 | 0 | <1 |
| RNA splicing | SF3B1 | 6 | 0 | | 93 |
| | SFSR2 | 46 | 0 | | 7 |
| | U2AF1 | 5 | 0 | | 7 |
| | ZRSR2 | 8 | 0 | | ~1 |
| Transcription | RUNX1 | 15 | 0 | 6 | 14 |
| | CEBPA | 4-20 | 4 | 4 |
| | NPM1 | 1-6 | 1 | 3 |
| | WT1 | ~1 | ~1 | |
| | TP53 | <1 | 0 | Rare | Rare |
| Cohesin complex | STAG2 | ~10 | |
| DNA methylation | DNMT3A | 2 | 0 | Rare | 4 | 15 |
| | TET2 | 58 | 0 | 30 | 30 | 25 |
| | IDH1/2 | 6 | 0 | Rare | 5-10 | |
| Histone modifications | ASXL1 | 40 | 0 | 69 | 15 |
| | EZH2 | 5 | 0 | 13 | 10 |
| | SUZ12 | 5 | 0 | Rare | Rare |
| | EED | >5 | Rare |
| | UTX | 8-9 |
Mutational spectrum of MDS/MPNs

Most recurrent genetic mutations affect genes involved in one of four functional categories: signaling, splicing, transcription, and epigenetic. The annotation of these mutations has provided insight regarding the dysregulated pathways that could be responsible for the paradoxical dual phenotype characteristic of MDS/MPN. Signaling mutations, typically seen in MPNs, lead to dysregulation of proliferative and anti-apoptotic pathways, and include mutations of growth factor receptors (CSF3R), downstream cytokine receptor signaling intermediates (JAK2, NRAS, KRAS) and negative regulators of signaling pathways (PTPN11, CBL, NF1). Additional epigenetic mutations include IDH1/2, EZH2, DNMT3A, SUZ12, EED, and UTX. Mutations of genes involved in RNA splicing are also common in MDS/MPN and are critically important in the phenotypic presentation of these patients. Specifically, the presence of SRSF2 mutation, the most common spliceosome mutation in CMML, in combination with TET2 has been found to be highly specific for monocytosis and associated with CMML while SF3B1 mutation is tightly concordant with the presence of bone marrow ringed sideroblasts in RARS-T.

Diagnostic considerations

Diagnostic criteria of MDS/MPNs are primarily clinicopathologic and the specific 2008 WHO criteria are listed below (Table 2). By definition, MDS/MPN includes phenotypic properties of both MDS and MPNs, and the potential cases hence require a discerning diagnostic evaluation to assure they do not belong to one of those respective categories. In addition, the detection of monocytosis allows for the recognition of CMML and JMML while the diagnosis of aCML and MDS/MPN-U is more challenging due to the increased difficulty of distinguishing them from other MPNs. A particular challenge in the diagnosis of CMML is excluding other causes of monocytosis, especially because the diagnosis does not require the presence of dysplasia and may be based solely on

| Table 2 WHO defined diagnostic criteria for MDS/MPN classification |
|---------------------------------------------------------------|
| **CMML** | **JMML** | **aCML** | **MDS/MPN-U and RARS-T** |
| Persistent peripheral blood monocytosis >1×10⁹/L | Peripheral blood monocytosis >1×10⁹/L | WBC >13×10⁹/L with increased and dysplastic neutrophils | Features of MDS category and <20% blasts in blood and bone marrow |
| No BCR-ABL or PDGFR fusion gene | No BCR-ABL or PDGFR fusion gene | No BCR-ABL or PDGFR fusion gene | Prominent myeloproliferative features |
| <20% blasts in the blood and bone marrow | <20% blasts in the blood and bone marrow | <20% blasts in the blood and bone marrow | No preceding history of MPN or MDS, no recent cytotoxic or growth factor therapy |
| Dysplasia in one or more lineages, if no dysplasia then: | Two of the following must be present: | Minimal absolute basophilia | No BCR-ABL or PDGFR or FGFR fusion and no isolated del(5q), chr 3 inversion or Features of mixed MDS |
| · An acquired clonal cytogenetic or genetic abnormality | · Hemoglobin F increase | No or minimal monocytosis | MPN and cannot be assigned MDS, MPN or MDS/MPN Category |
| · The monocytosis has persisted for >3 months | · Immature granulocytes in peripheral blood | Hypercellular BM with granulocyte dysplasia | RARS-T: |
| · All other causes of monocytosis have been excluded | · WBC >10×10⁹/L | Neutrophil precursors >10% of leukocytes | · Platelet count >450×10⁹/L |
| | · Clonal chromosome abnormality | in vitro | · 15% ring sideroblasts in the bone marrow |
| | · GM-CSF hypersensitivity of myeloid progenitors in vitro | | · Presence of megakaryocytic atypia resembling EF or MF |
monocytosis that is unlikely to be caused by a concomitant condition. Although cytogenetic abnormalities occur in only 30% of CMML cases, recent data revealed that sequencing of only 9 genes identifies clonality in 93% of cases, and thus the incorporation of targeted next-generation sequencing (NGS) can potentially aid in clarifying cases with diagnostic uncertainty. In addition, to the end of discerning CMML from other myeloid neoplasms with monocytosis, a monocytic subset restriction has been identified in CMML that is not seen in other causes of monocytosis including other neoplasms. This technique, which has been externally validated and shown to be highly sensitive and specific, relies on flow cytometry and thus could be incorporated into clinical practice.

There are several diagnoses that must be excluded in the evaluation of the potential cases of MDS/MPN. In the case of predominant monocytosis and consideration of CMML or JMML, reactive causes of monocytosis including infection, inflammatory disorders, and nutritional aberrances, must be excluded. Furthermore, a blast percentage greater than 20 in the peripheral blood or bone marrow, or the presence of acute myeloid leukemia (AML)-defining mutations, would confirm the diagnosis of AML. To exclude the diagnosis of CML, BCR-ABL1 fusion gene must be tested in all cases. When eosinophilia is present, rearrangements of PDGFR and FGFR should be assessed for to exclude myeloid and lymphoid neoplasms with rearrangements of PDGFR, PDGFRB, and FGFR. However, we have reported on a patient with refractory CMML without eosinophilia who harbored a PDGFRB fusion gene and given the therapeutic indications should consider more generalized testing. A general approach to diagnosis is diagramed in Figure 1.

**General prognostic and treatment considerations**

As a group, these disorders have a poor prognosis with limited treatment options. Regarding prognostication, CMML is the only MDS/MPN subtype whose prognostication has been extensively interrogated. In fact, at least 7 clinical and 2 genetic (incorporating ASXL1) prognostic models have been developed for CMML, and have all recently been validated in an analysis of an international CMML database of over 1800 patients. However, no model was demonstrated to be statistically superior, and thus, no consensus prognostic score has been established. RARS-T has been considered an indolent disease relative to the other MDS/MPN subtypes, but emerging data from mutational annotation suggest a worse prognosis in patients who are wild-type for SF3BI and JAK2. Although no prognostic scoring system has been developed for aCML, a worse prognosis was seen in patients with mutation of SETBP1, with a median overall survival (OS) of 22 months compared to 77 months in wild-type patients. The lack of prognostication with regards to MDS/MPN-U is likely complicated by the category’s inherent diagnostic uncertainty.

The majority of treatment recommendations are extrapolated from clinical trials focused on MDS or MPN patients and thus include very few overlap syndrome patients. Although several pharmacologic agents have demonstrated activity, none have shown effect on the natural history of the diseases. Therapeutic strategies are largely directed at alleviating the predominant myelodysplastic or myeloproliferative features manifested in individual cases. Hypomethylating agents (HMAs) such as azacitidine and decitabine are typically used when cytopenias predominate. Approaches to the management of predominant myeloproliferative symptoms include cytoreductive agents such as hydroxyurea, as well as etoposide, topotecan, arsenic, all-trans retinoic acid, and induction chemotherapy.

In addition to diagnostic and prognostic utility, mutational profiling also has potential treatment implications as it can identify patients who may benefit from targeted therapy, particularly given the rapid and ongoing development of targeted agents. For example, the presence of TET2 or DNMT3A mutations has been shown to predict better response to the treatment with the DNMT inhibitors/HMAs azacitidine and decitabine in a mixed cohort of patients with myeloid disease, including patients with MDS-MPN. In a cohort of MDS patients, mutation of TET2 was also shown to be a strong predictor of response to HMAs, particularly in patients without ASXL1 mutations. In addition, more recent work has highlighted that differentially methylated regions (DMR) can predict response to decitabine, and utilizing an epigenetic classifier derived from methylation profiles could predict decitabine response at the time of diagnosis. Additional DNMT inhibitors are in pre-clinical and clinical investigation and ideally will be evaluated in the context of specific biomarkers to enrich for response. Other novel pharmacologic treatments currently under investigation include JAK inhibitors, SRC inhibitors, and MEK inhibitors. Allogeneic stem cell transplantation (allo-SCT) is supported by data demonstrating potential for improved survival and cure.
**CMML**

CMML is a clinically and pathologically diverse clonal hematopoietic malignancy defined by a hematologic phenotype of peripheral monocytosis and dysplasia.

Although previously considered a subtype of the MDS, it was reclassified by the WHO in 2008 into the category of MDS/MPN. The incidence of the disease is 1/100,000 adults, with a median age at diagnosis of 65-75 years and a male predominance of 1.5-3:1. By definition, there is an absence of the BCR-ABL1 fusion gene, as well as rearrangements of PDGFR and FGFR1. The disorder may occur secondarily in...
rare instances in the setting of MDS or myelofibrosis. The pathognomonic feature of CMML is an expanded peripheral monocytes (>1×10^9/L), and while myelodysplasia is also a characteristic feature, its presence is not required for diagnosis if there is persistent monocytes (>3 months) or if a clonal cytogenetic or molecular genetic abnormality is present. While the diagnosis is dependent on laboratory, morphological, and clinical parameters, data on the molecular profile of the disorder has expanded recently and is now incorporated into the diagnostic process. Other causes of monocytes that should be excluded in the evaluation of CMML include pregnancy, autoimmune disorders, major depression, drugs (e.g. corticosteroids or colony stimulating factors), infection, and inflammation.

Peripheral monocytes present in CMML often have an abnormal morphologic appearance with bizarre nuclei and cytoplasmic granules. At diagnosis, patients typically exhibit leukocytosis but may present a normal or slightly decreased leukocyte count with variable neutropenia. Common clinical features include splenomegaly and hepatomegaly, particularly in patients with leukocytosis. In addition, extramedullary leukemic infiltration may involve the skin and lymph nodes.

Clonality can be established in most cases of CMML through detection of recurrent genetic mutations which involve a heterogeneous array of pathways including signal transduction (NRAS, KRAS, CBL, JAK2), DNA methylation (DNM3TA, TET2, IDH1/2), transcriptional regulation (ETV6, RUNX1), chromatin modification (EZH2, ASXL1), and the RNA splicing machinery (SF3B1, SRSF2, ZRSR2, U2AF1). In fact, by sequencing only 9 genes, a genetic clonal event can be identified in over 90% of CMML cases.

The most frequently identified mutations include TET2 (50%–60%), ASXL1 (35%–40%), SRSF2 (40%–50%), and RUNX1 (10%–15%). In addition, the co-mutation of SRSF2 and TET2 appears to be highly specific for CMML phenotype, and thus can be diagnostically useful (particularly in cases with a relative monocytosis). CMML exhibits a poor overall prognosis with a median OS of 20–30 months and leukemic transformation rates of 15%–20% in patients. The majority in risk models are based on MDS studies and were formed prior to the use of HMA. CMML is stratified into two groups, CMML-1 and CMML-2 by the current WHO classification according to the number of blasts present in the peripheral blood and bone marrow.

Patients in the CMML-2 group have been shown to have worse median survival (15 months compared to 20 months in CMML-1) and are more likely to progress to AML. Assessment of cytogenetic abnormalities has identified a high risk group that includes the presence of trisomy 8, chromosome 7 abnormalities, or a complex karyotype. The prognostic implication of genetic mutations has also been investigated, and incorporation of molecular data has recently led to improved prognostic discrimination in CMML. This is demonstrated by two models which investigated the prognostic value of integrating molecular lesions along with other clinical variables. On multivariate analysis, the mutation of ASXL1 was found by both models to be the only mutation independently predictive of survival. In analysis of the largest CMML database created to date, the negative prognostic impact of ASXL1 was validated along with identifying mutation of CBL to have a negative prognostic impact.

Mutation of SETBP1 has also been confirmed to have independent prognostic value in CMML.

There have been few clinical trials specifically designed for CMML and treatment for this disease is largely targeted at the alleviation of symptoms. The only randomized clinical trial published in CMML to date evaluated hydroxyurea versus etoposide with improved survival and response rates.

**Table 3** GFM and Mayo molecular prognostic models

| GFM CMML Model | Score | OS (months) | AMLFS |
|----------------|-------|-------------|-------|
| Low            | 0-4   | Not reached | 56.0  |
| Intermediate   | 5-7   | 38.5        | 27.4  |
| High           | 8-12  | 14.4        | 9.2   |

| Mayo prognostic model | Risk     | Score | OS (months) |
|-----------------------|----------|-------|-------------|
| Low                   | 0        | 97    |
| Intermediate-1        | 1        | 59    |
| Intermediate-2        | 2        | 31    |
| High                  | ≥3       | 16    |

Score 3 for WBC >15×10^9/L, and 2 for each of age >65, anemia (Hgb <10 g/dL in females, <11 g/dL in males), platelets <100×10^9/L, and ASXL1 mutation

Abbreviations: GFM = Groupe Francophone des Myelodysplasies; OS = overall survival; AMLFS = AML-free survival, Hgb = hemoglobin
in the hydroxyurea arm. Allo-HCT remains the only potentially curative therapy. One of the largest HCT trials for CMML included 85 patients and demonstrated a 10-year OS of 40%, and identified CMML risk group (1 vs. 2), pre-transplant hematocrit, cytogenetic risk category, comorbidity index, and age as factors associated with favorable outcome. A recent retrospective study identified splenomegaly as a negative predictor of OS and event free survival following allo-HCT.

There is no consensus on the optimal treatment strategy for patients not eligible for transplant. Although HMAs (e.g. azacitidine/decitabine) are typically the preferred pharmacologic treatment option for patients with symptomatic cytopenias, it remains unclear if these agents are disease modifying. In recent phase 1 and 2 trials, HMAs have resulted in response rates in CMML comparable with those in MDS. The Groupe Francophone des Myelodysplasies (GFM) is running a phase 3 trial comparing decitabine +/- hydroxurea to hydroxyurea alone to address the question of the optimal first line therapy for these patients. A recent phase 1 trial of the JAK inhibitor ruxolitinib demonstrated efficacy, particularly in patients with splenomegaly and constitutional symptoms, thus confirming the JAK/STAT pathway as a therapeutic target in CMML. The phase 2 portion of the trial is actively accruing. Additional cytoreductive agents that have shown efficacy at palliating proliferative or constitutional symptoms include topotecan and etoposide as single agents or in combination with cytarabine.

**JMML**

JMML is a rare clonal hematopoietic malignancy of childhood and its key feature is proliferation of monocytic and granulocytic lineages. JMML comprises under 2%–3% of all childhood leukemias and most frequently occurs in children less than 3 years of age, with a male-to-female ratio of approximately 2:1. An increased risk of developing JMML is seen in children with the congenital syndromes of neurofibromatosis 1 (NF1) and Noonan syndrome which converge on RAS signaling abnormalities. The clinical trajectory is heterogeneous, resulting in a fulminant course refractory to treatment in some patients, while those with Noonan syndrome may have spontaneous resolution despite the detection of clonal hematopoiesis. Leukemic transformation can be seen in JMML, but it is much less common than in adult myeloid malignancies. Overproduction of monocytic and granulocytic cells leads to infiltration of various organs including the spleen, liver, lung, skin, and gastrointestinal tract, with consequent substantial morbidity and mortality. Other characteristic clinical features include fever, thrombocytopenia, and hemoglobin F elevation. Clinical and laboratory findings may mimic infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV), which must be excluded prior to the diagnosis of JMML.

Over 90% of patients with JMML harbor somatic or germline mutations of PTPN11, NF1, N-RA, K-RA, or CBL. All of these genes encode proteins that signal through the RAS-RAF-MAPK pathways. Germline mutations of these genes have been identified in patients with congenital genetic syndromes, namely NF1 in patients with neurofibromatosis 1, and PTPN11 in patients with Noonan syndrome. Recently, through the use of exome sequencing, secondary mutations of SETBP1 and JAK3 were identified in around 15% of patients and were associated with poorer outcomes. Interestingly, a molecular hallmark of JMML present in most patients is marked hypersensitivity of myeloid progenitor cells in vitro to granulocyte-macrophage colony-stimulating factor (GM-CSF), which appears to augment signaling of other downstream effectors, particularly JAK/STAT, despite virtually universal dysregulation of RAS.

JMML remains an aggressive and rapidly fatal disease if patients are left untreated, with a median survival of around one year. Leukemic transformation is not common in JMML and patients without treatment generally succumb to respiratory failure due to leukemic infiltration of the lungs. Recent investigation of epigenetic abnormalities has shown CpG island hypermethylation to be strongly associated with older age, elevated fetal hemoglobin, and poorer prognosis. In another study, methylation of RASA4 isoform-2 promoter correlated with clinical parameters predictive of poor prognosis, PTPN11 mutation, and higher risk of relapse after allo-SCT.

The mainstay approach to treatment is allo-SCT which leads to event-free 5-year survival in about half the patients. Despite the substantial cure rate, relapse is a significant problem and is the major cause of treatment failure, occurring in nearly 50% of patients. Half of patients who relapse, however, can be rescued with a second allograft. Overall, strategies to rescue patients after relapse remain suboptimal, including the limited success of donor lymphocyte infusions (DLI).

Current non-transplant alternatives are also limited and efforts are underway to target underlying mutations. Specifically, targeting the RAS pathway has had limited...
success so far. The HMA azacitadine has been shown to lead to molecular and hematologic remissions in a small number of patients with JMML, and requires further investigation to determine its usefulness in the pre-transplant and non-transplant settings. Investigation of treatment with MEK, JAK, and SRC inhibitors, as well as low-dose chemotherapy and HMAS, as is actively ongoing. Children with JMML with mutations of CBL often have spontaneous resolution of their disease and can typically be actively monitored instead of being treated with allo-SCT.

**aCML**

Atypical chronic myeloid leukemia is an extremely rare BCR-ABL1-negative myeloid neoplasm with an estimated incidence of 1% of typical BCR-ABL1-positive CML. The median age is over 60 years, with approximate equal male-to-female distribution. It is characterized by a hypercellular bone marrow which results in leukocytosis (>13×10^9/L) composed predominantly of morphologically dysplastic neutrophils and their precursors. Additional key diagnostic requirements include absence of BCR-ABL1, PDGFR and FGR1 rearrangements, and no significant monocytosis (<10% of leukocytes) or basophilia (<2% of leukocytes). Other clinical characteristics include severe anemia, thrombocytopenia, and splenomegaly.

Multiple recurrent mutations have been described in aCML, including NRAS, KRAS,JAK2V617F, TET2, and CBL, although none are specific to aCML. Mutations of SETBP1 were found in 25% of aCML cases and were associated with a worse prognosis, but have also been described in other myeloid malignancies including CMMI. Mutations of CSF3R, the gene encoding the receptor of colony stimulating factor 3, were recently detected in about 40% of patients with aCML and 90% of those with chronic neutrophilic leukemia (CNL). Membrane proximal mutations (T618I) were the most common in aCML patients although truncating mutations of the cytoplasmic tail and compound mutations were also seen. However, more recent investigations suggest proximal mutations to be highly sensitive and specific for CNL as 46 aCML patients in these studies were all negative for CSF3R mutation.

Overall prognosis is poor with the median survival of aCML patients ranging from 2 to 3 years. Leukemic transformation occurs in around 40% of cases and the remainder of patients typically succumb to bone marrow failure. As with other MDS/MPNs, there is no standard treatment, and allo-SCT appears to be the only strategy that offers a potential long-term remission although data is extremely limited due to the low incidence of the disease.

**MDS/MPN-U**

MDS/MPN-U is the most heterogeneous and least well characterized MDS/MPN subgroup which includes patients with features of both MDS and MPN but lacking defining characteristics of the other subtypes. Incidence of MDS/MPN-U is not well known, but it is estimated to make up around 5% of all myeloid malignancies. Two recent series of MDS/MPN-U patients have provided insight into biological and clinical features of the disorder. Median age at diagnosis is 71 years and there is a male predominance of about 2:1. Other common characteristics include splenomegaly, low monocyte counts, 20%-30% -positive, and non-specific cytogenetic findings.

There are no currently recognized specific cytogenetic or molecular features for MDS/MPN-U, and cytogenetic studies in cases of MDS/MPN-U mainly serve to exclude other similar disorders. For example, cases with mutations involving SF3B1, CSF3R, T618I, or CALR are assigned to specific MDS/MPN subgroups, and are excluded from categorization as MDS/MPN-U. Despite the lack of specific mutations, molecular overlap is seen with aCML as mutations of SETBP1 can also be seen in around 10% of MDS/MPN-U cases.

Overall median survival of MDS/MPN-U patients varied among two series: 12.4 months vs. 21.8 months. Most clinical and pathologic features were similar among the two groups, but a higher proportion of patients in the series with inferior survival were noted to have thrombocytopenia, possibly representing a more aggressive phenotype with poorer prognosis. In addition, AML-free survival was 18.9
months in the Orazi group, but not reported in the other series. There is currently no consensus on optimal treatment for MDS/MPN-U patients who are ineligible for allo-SCT. In the largest series of MDS/MPN-U patients to date, those treated with HMAs demonstrated a superior OS compared with patients with other non-transplant treatments (16.4 months vs. 11.5 months). Other pharmacologic treatments include interferon alpha, cyclosporine, thalidomide, lenalidomide, and anti-thymocyte globulin.

RARS-T

RARS-T is a provisional entity in the WHO 2008 classification characterized by MDS features of refractory anemia with ring sideroblasts (>15% of erythroid precursors) along with thrombocytosis (>450×10⁹/L) associated with the proliferation of large atypical megakaryocytes resembling essential thrombocythemia. Median age of presentation ranges from 71 to 75 years with an almost equal distribution among the sexes. Features that support the inclusion of RARS-T into the hybrid MDS/MPN category are the commonly identified MPN-associated gene mutations (JAK2V617F and MPL) and MDS-like demonstrated poor in vitro colony forming capacity.

Recent characterization of the mutational landscape in RARS-T has broadened the understanding of the underlying pathogenesis. Mutation of the spliceosome gene SF3B1 is identified in up to 90% of patients with RARS-T, and is likely responsible for the induction of ringed sideroblasts, ineffective erythropoiesis, and anemia. Mutation of JAK2V617F is another molecular hallmark of RARS-T, as it occurs in approximately 50% of cases and is associated with significantly higher platelet counts. Presence of a JAK2V617F mutation is an important molecular characteristic of RARS-T as it is not seen in patients with RARS. Interestingly, SF3B1 wildtype patients exhibited co-mutation of ASXL1 and JAK2V617F or ASXL1 and other spliceosome mutations (U2AF1/SRSF2) in the majority of cases. Combined, one of these 5 mutations is present in 99% of RARS-T cases. Regarding prognosis, improved OS was demonstrated in patients with SF3B1 and/or JAK2V617F mutations when compared with wildtype patients of 6.9 versus 3.3 years. Furthermore, age (≤80 years) was also identified as a predictor of survival, and these three factors were incorporated into a prognostic model, with a median survival of 1.6 vs. 8.0 years in the high and low risk groups, respectively.

There is little data pertaining to the treatment of RARS-T and no optimal strategy has been established. Thus, therapeutic approaches are mainly derived from management of RARS and cytoreductive strategies for MPNs. Recent reports of treatment with lenalidomide have demonstrated benefit both in regards to cytopenias and splenomegaly. Other potential strategies include JAK2 inhibitors patients with proliferative symptoms. Spliceosome inhibitors should enter clinical investigation in the near future and can potentially exploit the haplodeficient state with the prospect of selective synthetic lethality. In addition, luspatercept is a fusion protein (modified activin receptor IIB-IgG Fc) that inhibits SMAD2/3 signaling, and is currently undergoing placebo-controlled, phase 3 evaluation in MDS patients with ringed sideroblasts as phase 2 data highlighted efficacy in this patient population. There is no recommendation regarding the use of aspirin or platelet-suppressive therapy, but given the recent report of increased risk of thrombotic events in RARS-T patients with SF3B1 mutations, low-dose aspirin therapy could be considered in these and cases of JAK2 mutated patients.

Conclusions

The category of MDS/MPN overlap disorders comprises a heterogeneous group of diseases that share a common paradoxical phenotype of concomitant myeloid subset proliferation and bone marrow failure. Although their categorization is currently based mainly on morphology, ongoing efforts to understand the molecular characteristics of these entities continue to uncover a complex underlying molecular pathogenesis responsible for the observed hybrid phenotypes. These advances have started to augment our diagnostic and prognostic capabilities, but our ability to alter the course of the disease outside of allo-SCT remains extremely limited. Further investigation is needed in order to refine our understanding of these aggressive diseases, expand the available therapeutic armamentarium, and ultimately improve the clinical care of MDS/MPN patients. Given the rapidly expanding identification of mutations within MDS/MPNs along with the ongoing development of novel targeted therapies, future treatment will likely be designed to address these underlying pathway drivers. Due to the rarity of these disorders, however, collaborative multicenter trials will likely be required for definite answers.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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