Myelodysplastic/ Myeloproliferative Neoplasms

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75.1 Definition, Epidemiology, Diagnosis, and Classification

The myelodysplastic syndrome-myeloproliferative neoplasms (MDS/MPNs) are a heterogeneous group of hematologic malignancies characterized by dysplastic and myeloproliferative clinical, laboratory, and morphological overlapping features, both in marrow and in blood. The MDS/MPN category, recently updated by the last revision to the WHO classification of myeloid neoplasms and acute leukemia (Arber et al. 2016), includes chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T), as well as unclassifiable forms of mixed myelodysplastic/myeloproliferative disorders (MDS/MPN-U) (Table 75.1).

While JMML affects only children from birth up to 14 years of age (median age at diagnosis 2 years), with an estimated incidence of approximately 1.2 cases per million annually

(Chang et al. 2014), adulthood MDS/MPN are typically diagnosed in elderly age with CMML being definitely the most frequent subtype (incidence of around 1 case/100,000 inhabitants per year, median age 70 years) (Solary 2014). Being very uncommon, data concerning the incidence of aCML, MDS/MPN-RS-T, and MDS/MPN-U are currently unknown.

75.2 Risk Factors and Prognostic Index

The clinical course of MDS/MPN varies from an indolent course over several years for a minor fraction of patients with CMML and MDS/MPN-RS-T to a more rapid progression with dismal prognosis and frequent transformation into secondary acute myeloid leukemia in the preponderance of patients with CMML and in the vast majority of patients with aCML and MDS/MPN-U, for whom allo-HSCT still represents the only curative option (Onida and Beran 2008; Onida 2017). Alike, long-term survival in the greater part of children with JMML may only be achieved by means of allo-HSCT.

CMML is highly heterogeneous, with clinical and hematological characteristics varying from mainly myelodysplastic to predominantly myeloproliferative. Based on marrow and peripheral blood blast percentage, the last WHO classification recognized three disease subtypes

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Table 75.1 Classification and diagnostic criteria of MDS/MPNs

Disease	Blood findings	Bone marrow findings
Chronic myelomonocytic leukemia (CMML)	Monocytes $\geq 1 \times 10^9/L$, ($\geq 10\%$ of the WBC) <20% blasts (1)	<20% blasts ^a Dysplasia in one or more myeloid lineages ^b <i>No evidence of BCR/ABL1, PDGFRA, PDGFRB, or FGFR1 rearrangement or PCM1-JAK2</i>
Atypical chronic myelogenous leukemia (aCML)	Leukocytosis due to increased numbers of neutrophils with IMC, $\geq 10\%$ of WBC Basophils <2%, Monocytes <10% <20% blasts Dysgranulopoiesis	<20% blasts Dysgranulopoiesis Hypercellularity, with granulocytic proliferation and granulocytic dysplasia, $\pm$ dysplasia in the erythroid and megakaryocytic lineages <i>No evidence of BCR/ABL1, PDGFRA, PDGFRB, or FGFR1 rearrangement or PCM1-JAK2</i>
Juvenile myelomonocytic leukemia (JMML) ^c	Monocytes $\geq 1 \times 10^9/L$, ($\geq 10\%$ of the WBC count); <20% blasts	<20% blasts <i>The absence of BCR/ABL1 rearrangement^d</i>
MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T)	Anemia, $\geq 15\%$ ring sideroblasts, platelet count $\geq 450 \times 10^9/L$ <1% blasts	Erythroid lineage dysplasia with or without multilineage dysplasia, <5% blasts The presence of a <i>SF3B1</i> mutation or, in its absence, no history of recent cytotoxic or growth factor therapy that could explain the MD/MP features <i>No rearrangement of BCR/ABL1, PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2. No (3;3) (q21;q26), inv(3)(q21q26) or del(5q)</i>
MDS/MPN unclassifiable (MDS/MPN-U) ^e	<20% blasts	<20% blasts

IMC immature myeloid cells (promyelocytes, myelocytes, metamyelocytes)

^aIncluding monoblasts and promonocytes

^bIf myelodysplasia is absent or minimal but other requirements are met, an acquired clonal cytogenetic or molecular genetic abnormality should be identified, or a nonreactive monocytosis persisting at least 3 months should be observed

^cSplenomegaly is a mandatory feature

^dPlus genetic abnormality (at least one) or additional criteria (Arber et al. 2016—Table 14)

^eMyeloid neoplasms with mixed proliferative and dysplastic features that do not meet the criteria for CMML, aCML, JMML, or MDS/MPN-RS-T are classified as MDS/MPN-U

(CMML-0, CMML-1, and CMML-2), associated to a corresponding decreasing life expectations (Arber et al. 2016). Over the latest years, a number of disease-specific prognostic systems have been developed in CMML in order to allow the best treatment strategy allocation (Onida 2017). The most recent ones are listed in Table 75.2.

Atypical CML, also named as BCR-ABL-negative CML, is a rare hematologic malignancy with an overall dismal prognosis (median 24 months). Age, hemoglobin level, and leukocyte count have been identified as variables with independent prognostic significance, allowing the stratification of two groups with significantly different life expectations. Likewise, for MDS/MPN-RS-T, three risk categories of patients were recently differentiated by a Mayo Clinic prog-

nostic model including molecular investigations (Table 75.2).

With regard to the JMML, acquisitions from modern genetic studies assign uncommon treatment indication in patients with germ line *PTPN11* and *CBL* mutations, who frequently experience spontaneous disease regression. In contrast, patients with neurofibromatosis type 1, somatic *PTPN11*, *KRAS*, and most of those with *NRAS* mutations require early allo-HSCT as a result of rapidly progressive disease (Hasle 2016).

MDS/MPN-U is the most heterogeneous and the least well-characterized entity, with no currently recognized specific molecular findings. Some description of the biological and clinical characteristics have been recently reported in two series (DiNardo et al. 2014; Wang et al. 2014),

Table 75.2 Prognostic systems in MDS/MPN

MDS/MPN	Prognostic model	Variables included [score]	Risk groups	Median OS (months)
CMML	GFM (Itzykson et al. 2013)	Age > 65 years [2] WBC >15 × 10 ⁹ /L [3] PLT <100 × 10 ⁹ /L [2] Anemia (F < 10 g/dL, M < 11 g/dL) [2] ASXL1 mutation [2]	Low (score ≤ 4) Intermediate (score = 5–7) High (score ≥ 8)	Not reached 38.5 14.4
	CPSS (Such et al. 2013)	WBC ≥13 × 10 ⁹ /L [1] WHO CMML-2 subtype [1] CMML-specific CG ^a inter/high [1/2] Transfusal dependency [1]	Low (score = 0) Intermediate-1 (score = 1) Intermediate-2 (score = 2–3) High (score = 4–5)	72 31 13 5
	MMM (Patnaik et al. 2014)	Hb <10 g/dL [2] AMC >10 × 10 ⁹ /L [2] Circulating IMC >0% [2] PLT <100 × 10 ⁹ /L [1.5] ASXL-1 Mut (frameshift/nonsense) [1.5]	Low (score = 0) Intermediate-1 (score = 1.5–2) Intermediate-2 (score = 2.5–4.5) High (score ≥ 5)	97 59 31 16
	CPSS-Mol (Elena et al. 2016)	WBC ≥13 × 10 ⁹ /L [1] BM blasts ≥5% [1] Genetic risk group ^b [score 0 to 3] Transfusal dependency [1]	Low (score = 0) Intermediate-1 (score = 1) Intermediate-2 (score = 2–3) High (score ≥ 4)	Not reached 64 37 18
aCML	MDACC (Onida et al. 2002)	Age > 65 years [1] Hb ≤10 g/dL [1] WBC >50 × 10 ⁹ /L [1]	Low (score = 0–1) High (score = 2–3)	38 9
MDS/MPN-RS-T	Mayo (Patnaik et al. 2016)	Hb <10 g/dL [1] CG abnormalities [2] ASXL-1 mutation [1] SETBP1 mutation [1]	Low (score = 0) Intermediate (score = 1) High (score ≥ 2)	80 42 11

^aCMML-specific cytogenetic risk classification, low, normal, and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7

^bgenetic risk group, CMML-specific cytogenetic risk classification + ASXL1/NRAS/SETBP1 mutation (score = 1)/RUNX1 mutation (score = 2)

with median survival of 12.4 and 21.8 months, respectively, and possible association of thrombocytosis with a more favorable outcome.

control rather than the achievement of disease remission (Odenike et al. 2015).

75.3 Pretransplantation Treatment

For this rare group of diseases, there are only few prospective studies on therapy, most being either retrospective analyses or case reports, making it difficult to give recommendations. In general, because apart from allo-HSCT no therapy has been shown to modify the disease course, pretransplantation treatments point toward symptom

75.3.1 CMML

In general, treatment strategies in patients with CMML with symptomatic or progressive disease are based on the dysplastic versus proliferative features and the percentage of marrow blasts (Onida et al. 2013). In the presence of rising leukocytosis and/or organ infiltration (mostly splenomegaly) with low marrow blast percentage, hydroxyurea (HU) remains the drug of choice. Patients showing high blast percentages may be

bridged to transplant through AML-like induction chemotherapy or by means of hypomethylating agents (HMAs), with a reported 20–50% overall response rate. In a recent retrospective study including a relatively small number of patients, HMAs have been suggested to increase progression-free survival (PFS) through the reduction of post-transplantation relapse rate (Kongtim et al. 2016). Treatment strategies based on the combination of HMAs with other agents (e.g., lenalidomide) and the advent of new targeted therapies such as JAK2 inhibitors or poly(ADP-ribose) polymerase (PARP) inhibitors may further increase the response rate leading to an overall improvement of post-transplantation outcomes.

75.3.2 aCML

Due to its absolute rarity in patients having no age or comorbidity barrier to allo-HSCT, no consensus subsists on to whether any pretransplant treatment may have an impact on post-transplantation outcome and what kind of therapy should be best used. Control of leukocytosis is generally achieved with cytoreductive agents such as HU or IFN- α immunomodulation. Chemotherapy induction treatment is preferred when facing high blast count in advanced disease phases or in patients showing AML transformation.

Some efficacy of decitabine and of ruxolitinib single agent has also been reported, whereas a phase II trial of AZA and ruxolitinib in combination in a series of 35 MDS/MPN patients showed promising activity, with an overall response rate of 57% according to the 2015 international consortium response criteria for MDS/MPN (Savona et al. 2015), even though median survival of the few aCML included patients ($n = 4$) was only 8 months (Assi et al. 2018). According to the most recent discovery, *SETBP1* and *ETNK1* mutations are present in 15–32% and up to 10% of aCML patients, respectively, whereas *JAK2* mutation is rare (0–7%), and *CSF3R* mutations are only occasionally observed. Even though in the near

future these findings may influence therapeutic approaches by means of evolving targeted therapies, currently allo-HSCT remains the only treatment strategy with established curative potential in eligible patients (Dao et al. 2017).

75.3.3 JMML

For JMML patients the possible therapeutic interventions prior to transplantation are rather scarce. Different chemotherapeutic agents have been used prior to transplant, but there is no consensus on to whether there should be any pre-transplant therapy and what type should be given. HMAs may have potential activity (Cseh et al. 2015), but data are too few to make any recommendation. Other potentially active agents include JAK, MEK, and SRC inhibitors, but clinical trial with these drugs is still on their way.

75.3.4 MDS/MPN-RS-T

MDS/MPN-RS-T generally represents the disease entity associated with the best prognosis among overlap syndromes, with a median survival of about 6 years (Broseus et al. 2012). Guidelines for disease management are not formally recognized, and treatment strategies are generally extrapolated from low-risk MDS and MPN, with adjusted individual management depending on presenting problems. While lenalidomide has been occasionally reported to reduce transfusion need, antiplatelet and cytoreductive treatments are often required due to the high risk of thrombosis. Based on the different gene mutations possibly involved (*SF3B1*, *JAK2*, *TET2*, *DNMT3A*), attentiveness in targeted therapies is developing.

75.3.5 MDS/MPN-U

MDS/MPN-U is a very rare and heterogeneous disease entity, with no consensus on which therapy (if any) should be given for patients candidate to allo-HSCT. Augmented leukocyte proliferation

is generally managed by means of cytoreductive agents such as HU or through immunomodulation with IFN α , while HMAs as well as lenalidomide may represent an option in case of prevailing cytopenias. JAK inhibitors are also potential therapeutic options, either alone or in combination with HMAs (Assi et al. 2018). When patients are progressing to AML transformation, induction chemotherapy should be used as a bridge to allo-HSCT.

75.4 Autologous HSCT

Because the harvesting of polyclonal hematopoietic progenitor cells is not feasible through the currently available treatment options, autologous HSCT is currently not a recommended strategy in MDS/MPN.

75.5 Allogeneic HSCT

Currently still representing the only curative strategy, the role of allo-HSCT in adult MDS/MPN patients remains controversial mainly due to the lack of prospective studies, being therefore generally considered a possible treatment option for eligible patients with high-risk diseases.

In CMML benefits and risks of allo-HSCT have been analyzed retrospectively in various series, with different characteristics at transplant and much variable outcomes described (Table 75.3). Recent recommendations from an international expert panel agreed to limit indication for allo-HSCT in CMML patients classified in the intermediate-2 and high-risk CPSS categories (de Witte et al. 2017), representing the preferred treatment modality for younger patients with acceptable comorbidity index (Patnaik et al. 2015).

Table 75.3 Summary of selected studies on allo-HSCT in CMML

Author (year)	Pt N.	Median age (range)	Disease type/ stage	Donor type	Conditioning (MAC vs RIC)	TRM/relapse rate	Survival outcome
Kröger et al. (2002)	50	44 (19–61)	CMML-1 = 28 CMML-2 = 17 Missing = 5	MRD = 43 MUD = 7	MAC = 50 RIC = 0	TRM = 52% RR = 28%	OS (5y) = 21% DFS (5y) = 18%
Eissa et al. (2011)	85	51 (1–69)	CMML-1 = 57 CMML-2 = 26	MRD = 38 MUD = 47	MAC = 58 RIC = 27	TRM (10y) = 35% RR (10y) = 27%	OS (10y) = 40% DFS (10y) = 40%
Park et al. (2013)	73	53 (27–66)	CMML-1 = 24 CMML-2 = 26 Missing = 23	MRD = 41 MUD = 32	MAC = 30 RIC = 43	TRM = 35% RR = 35%	OS (3y) = 32% DFS (3y) = 29%
Symeonidis et al. (2015)	513	53 (18–75)	CMML-1 = 87 CMML-2 = 32 s-AML = 95 Missing = 299	MRD = 285 MUD = 228	MAC = 249 RIC = 226	TRM (4y) = 41% RR (4y) = 32%	OS (4y) = 33% DFS (4y) = 27%
Kongtim et al. (2016)	83	57 (18–78)	CMML-1/2 = 47 sAML = 36	MRD = 30 MUD = 47 MMR = 6	MAC = 64 RIC = 19	TRM (3y) = 31% RR (3y) = 33%	OS (3y) = 35% DFS (3y) = 34%
Liu et al. (2017)	209	57 (23–74)	CMML-1 = 140 CMML-2 = 52 Missing = 17	MRD = 73 MUD = 127 MMUD = 9	MAC = 105 RIC = 99 Missing = 5	TRM (5y) = 28% RR (5y) = 52%	OS (5y) = 30% DFS (5y) = 20%
Itonaga et al. (2018)	159	54 (16–75)	Not reported	MRD = 51 MUD (BM) = 66 Cord = 30 MMR = 12	MAC = 92 RIC = 67	TRM = 28% RR = 39%	OS (3y) = 33%

As *aCML* is extremely rare in people younger than 65 years, outcome after allo-HSCT has been described only in small single-institution series. A 5-years OS and RFS of 51% and 36%, respectively, were recently reported by the EBMT-CMWP in a retrospective analysis of 42 patients transplanted between 1997 and 2006. With a RR of 40%, a better OS was recognized in young patients with low EBMT risk score (Onida et al. 2017).

With regard to *JMML*, 5-years OS and EFS out of 100 patients transplanted 1993 through 2002 within the EWO-MDS/EBMT trial were 64% and 52%, respectively, with a 5-years TRM of 13% (Locatelli et al. 2005). Overall, younger age, male sex, low HbF, and low BM blast percentage were associated to better survival. Early disease recurrence was the major cause of treatment failure, irrespective of donor type (sibling vs unrelated vs CB). Although both acute and chronic GvHD are associated with a lower relapse risk, DLI in *JMML* relapse is mostly unsuccessful. In contrast, a second HSCT with the same or an alternative donor may cure about 30% of the patients (Locatelli and Niemeyer 2015).

In *MDS/MPN-RS-T* allo-HSCT is generally not indicated, being reserved for patients developing refractory cytopenias or accelerated/blastic transformation (Sharma et al. 2017), whereas eligible patients with *MDS/MPN-U* should always be considerate as potential candidate for allo-HSCT due to the general dismal prognosis.

75.6 Source of HSC

No impact of HSC source on the transplant outcome has been observed in the largest CMML series reported by the EBMT-CMWP (Symeonidis et al. 2015). This was in contrast to the CIBTMR study, in which the survival was statistically better with PBMC than with BM, with no clear explanation outside the small proportion of BM transplants (16%) (Liu et al. 2017). The source of stem cell is therefore left open, but PBSC may potentially be preferred to decrease the risk of graft failure and the relapse risk, particularly with the use of RIC.

In the pediatric population, the majority of transplantation are done with BM, mainly due to the potential of decreasing the incidence of GVHD. In the largest series of *JMML* patients reported, BM was the stem cell source in 79% with no significant difference on the outcome in comparison to PBSC (Locatelli et al. 2005).

For *aCML*, *MDS/MPN-RS-T*, and *MDS/MN-U*, data are too scarce to make clear recommendations.

75.7 Conditioning and GvHD Prophylaxis

In *MDS/MPN* patients, the choice of conditioning regimen depends on many different conditions, the major ones being comorbidities, patient age, disease phase at transplant, type of donor, and HSC source. In the two largest retrospective series of CMML patients (Symeonidis et al. 2015; Liu et al. 2017), MAC and RIC were almost equal in proportion, with no outcome difference. Likewise, in the largest reported series of *aCML* patients, conditioning intensity had no impact on the outcome (MAC were used in 76%). Noteworthy, an improved outcome following a combined fractionated 6–8 Gray TBI/FLU conditioning regimen was recently reported in advanced CMML (Radujkovic et al. 2017).

In general, for young patients (<60 years), with a HSCT-CI (Sorrer et al. 2005) less than 2, MAC regimens such as BU-CY, TT/BU/FLU (TBF), or the reduced-toxicity FLU/BUx4 (FB4) may be advisable, particularly in the proliferative variant of CMML and in other *MDS/MPN* with predominant proliferative features, whereas a RIC regimen such as BU/FLU or reduced TBF may be preferred for patients with older age or comorbidities and for patients undergoing transplant with disease remission following pre-transplant treatment.

Facing an aggressive disease in a very young population, MAC regimens are generally preferred in *JMML*. In the biggest series published, the conditioning included CT, BU and MEL (Locatelli et al. 2005), with a 5-years OS of 64%. More recently, a conditioning containing BU,

FLU, and MEL showed promising results, with more than 50% of patients in remission after alternative donor transplantation (Yabe et al. 2015). Based on those data, the recommended conditioning for JMML patients should rely on the backbone of BU and MEL with either CY or FLU.

75.8 Maintenance/Post transplant Strategies

As disease recurrence represents the major cause of transplant failure in MDS/MPN, there is a growing interest toward post transplant strategies, although few data are currently available in this particular setting.

Indirect evidence of a graft versus CMML by a reduced incidence of relapse in patients with GvHD has been recently reported (Itonaga et al. 2018). Some effect of DLI has also been reported in patients with relapsing CMML and low disease burden.

With more molecular markers potentially available, cell therapy-based interventions may be planned on the base of residual or increasing MRD.

Potential interest both as preemptive and as maintenance strategy derive from the use of post transplant HMAs, alone or in combination with DLI, as reported in AML and MDS.

The use of lenalidomide and checkpoint inhibitors, but also JAK2 or PARP inhibitors, alone or even in combination, together with post transplant targeted therapies represents areas of growing interest under development.

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