74 Pediatric MDS Including Refractory Cytopenia and Juvenile Myelomonocytic Leukemia

Charlotte M. Niemeyer

74.1 Introduction

For pediatric patients with MDS and 2–19% blasts in the PB or 5–19% blasts in the BM, the same diagnostic criteria utilized for adults with MDS with excess blasts (MDS-EB) are applied (WHO). Some cases with 20–30% blasts may also have slowly progressive disease, may lack clinical features of acute leukemia, and thus behave more like MDS than AML. These cases of MDS-EB in transformation (MDS-EB-t) together with cases of MDS-EB account for approximately a quarter of all childhood MDS.

In the large cohort of children with MDS-EB/MDS-EB-t of the European Working Group of MDS in Childhood (EWOG-MDS), allo-HSCT with a full MAC consisting of the combination of BU/CY/MEL resulted in an OS at 5 years of 63%, with NRM and relapse contributing equally to treatment failure (Strahm et al. 2011). The update shows that the outcome for patients who received a graft from either a MSD or an UD matched for 9/10 or 10/10 HLA-loci by using high-resolution typing is superimposable (Locatelli and Strahm 2018). Because patients ≥12 years of age had a high risk of NRM, EWOG-MDS recommends an intensified GVHD prophylaxis (CSA + MTX) for older patients transplanted from a MSD (see http://ewog-mds.org). The presence of a structurally complex karyotype was found to be strongly associated with poor prognosis (Göhring et al. 2010).

74.2 Refractory Cytopenia of Childhood (RCC)

Most children and adolescents with MDS present with RCC, a provisional MDS entity characterized by persistent cytopenia and <5% blasts in the BM and <2% blasts in the PB (Baumann et al. 2017). BM biopsy shows considerable hypocellularity in about 80% of RCC cases. Most of these children with RCC have a normal karyotype and a low risk of progression to MDS-EB, while about 10–15% display an abnormal karyotype with monosomy 7, del(7q), or ≥2 aberrations.

It recently became evident that approximately half of all pediatric patients with primary MDS and monosomy 7 or del(7q) have GATA2 deficiency or SAMD9/SAMD9L syndrome (Wlodarski et al. 2016). Most of these children present as RCC. Since the presence of monosomy 7 is correlated with a high risk of progression to more advanced MDS, patients with monosomy 7 should generally receive HSCT as soon as possible. For RCC with monosomy 7, del(7q), or ≥2 aberrations, MAC is recommended. EWOG-MDS currently advocates a TREO-based regimen which results in prompt initial engraft-

C. M. Niemeyer (✉)
Department of Pediatrics and Adolescent Medicine, University Medical Center, Freiburg, Germany
e-mail: charlotte.niemeyer@uniklinik-freiburg.de

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ment with a low incidence of secondary graft failure and an OS of approx. 90% (see http://ewog-mds.org). Historical data with a BU/CY have provided an OS of approx. 75%, NRM being the major cause of treatment failure (Starý and Locatelli 2005).

In the absence of monosomy 7, RCC patients with mild cytopenia (no transfusion dependency for red cells or platelets and an absolute neutrophil count of $\geq 1 \times 10^9$/L) may have a stable course of disease and therefore qualify for a watch-and-wait strategy. For patients with more pronounced cytopenia, treatment is stratified according to cellularity.

In normo- or hypercellular RCC, a MAC regimen like that described for monosomy 7 may be utilized irrespective of karyotype. In patients with hypocellular BM, Fanconi anemia and dyskeratosis congenita should be excluded by chromosomal breakage and telomere length/molecular studies, respectively.

HSCT with a RIC is the treatment of choice for hypocellular RCC and normal karyotype (Inagaki et al. 2015; Strahm et al. 2007). HSCT with a preparative regimen of TT/FLU (Strahm et al. 2007) resulted in an OS of 94% and EFS of 88% (Strahm et al. 2017). However, approx. 10% of patients experience primary and secondary graft failure requiring a stem cell boost and/or second HSCT. Thus, EWOG-MDS currently recommends a preparative regimen of TREO/FLU aiming at an improved rate of engraftment (see http://ewog-mds.org). With a very low risk of disease recurrence, GVHD should be avoided; thus, BM is the preferred stem cell source combined with an effective GVHD prophylaxis (Locatelli and Strahm 2018). In the absence of a suitable donor, IST with horse ATG and CSA may be a therapeutic option in patients with hypocellular RCC and the absence of poor-risk karyotype (Yoshimi et al. 2014).

74.3 Juvenile Myelomonocytic Leukemia (JMML)

JMML is a unique clonal hematopoietic disorder of early childhood with myeloproliferative and myelodysplastic features (Locatelli and Niemeyer 2015). Splenomegaly, leukocytosis, monocytosis, and myeloid and/or erythroid precursors on PB smear are noted in close to all cases. Age ≥ 2 years, platelet count $<40 \times 10^9$/L, and a high hemoglobin F are poor prognostic factors.

JMML is characterized by hyperactivation of the RAS signal transduction pathway. About 90% of patients harbor molecular alteration in 1 of 5 genes (*PTPN11*, *NRAS*, *KRAS*, *NF1*, *CBL*) which define genetically and clinically distinct JMML subtypes. PTPN11-, NRAS-, and KRAS-mutated JMMLs are characterized by heterozygous somatic gain-of-function mutations in non-syndromic children, while JMML in neurofibromatosis type 1 (NF1) and JMML in children with CBL syndrome are characterized by germline RAS disease (RASopathy) and acquired biallelic inactivation of the respective tumor suppressor gene in hematopoietic cells.

JMML with somatic *PTPN11* mutations is a rapidly fatal disorder unless the patient undergoes HSCT. HSCT in JMML patients with *PTPN11* mutations is followed by a significantly higher relapse rate when compared to patients of the other JMML genetic subtypes. Like *PTPN11*-mutated disease, JMML in patients with *NF1* is fatal in the absence of HSCT.

Children with somatic heterozygous *KRAS* mutations (14%) often have a clinically particular aggressive form of disease. Close to all of these children require prompt HSCT. *NRAS*-associated JMML (16%) displays a great clinical diversity. While a considerable percentage of patients transplanted for JMML with *NRAS* mutations relapse after HSCT, others survive in the absence of HSCT with persistence of *NRAS* mutation but slowly regressing disease. Clinically these patients are well and show a normal or only slightly elevated HbF. Molecular studies suggest that children with *NRAS* mutation and spontaneous regression have a low methylation profile and no subclonal mutations.

The vast majority of children with *CBL*-mutated JMML myeloproliferation is self-limiting with splenomegaly decreasing over years without HSCT. In the absence of one of the five canonical RAS pathway alterations, rare mutations in other RAS genes and non-JMML

myeloproliferative disorders need to be excluded. Most of these cases require HSCT.

In JMML, allo-HSCT, either from a histocompatible sibling or from an HLA-matched/1-antigen-disparate URD, results in a DFS of 52% (Locatelli et al. 2005). Disease recurrence is the most important cause of failure, occurring with a cumulative incidence of 35%. UCBT is a suitable option for children lacking an HLA-compatible relative (Locatelli et al. 2013). Standard preparative regimen consists of BU/CY/MEL (Locatelli et al. 2005; Dvorak et al. 2018). While intensive chemotherapy prior to transplantation is generally not followed by durable responses, azacitidine might be an attractive option to bridge to HSCT (Cseh et al. 2015).

Key Points

- Most children and adolescents with MDS present with refractory cytopenia of childhood (RCC). In RCC, bone marrow cells often show a normal karyotype, and there is a low risk of progression to MDS-EB. In the presence of mild cytopenia and a hypocellular marrow, a watch-and-wait strategy may be appropriate; if HSCT is required, a preparative regimen with TREO/FLU results in prompt engraftment.
- In RCC with monosomy 7, del(7q), or ≥2 aberrations and in normo- or hypercellular RCC with any karyotype, MAC HSCT is recommended.
- JMML is characterized by hyperactivation of the RAS signal transduction pathway. About 90% of patients harbor molecular alteration in 1 of 5 genes (*PTPN11*, *NRAS*, *KRAS*, *NF1*, *CBL*) which define genetically and clinically distinct JMML subtypes.
- JMML with somatic *PTPN11* mutations is a rapidly fatal disorder in the absence of HSCT. Patients with *KRAS* mutations often have a clinically particular aggressive disease. *NRAS*-associated JMML displays a great clinical diversity, some patients have a slowly regressing disease in the absence of HSCT, while others relapse post HSCT. Most *CBL*-mutated JMML patients have a self-limiting myeloproliferation.
- The standard preparative regimen for HSCT in JMML consists of BU/CY/MEL.

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