Guidelines for Hematopoietic Stem Cell Transplantation (HSCT)
in Childhood MDS and JMML

EWOG-MDS Consensus Conference
Rome, February 2\textsuperscript{nd}, 2013

These guidelines were established and agreed upon by the EWOG-MDS HSCT Board during a Consensus Conference on February 2\textsuperscript{nd} 2013 in Rome.

Version 1.2, 01.09.2013
1. Refractory Cytopenia of Childhood (RCC)

1.1. Introduction

Refractory cytopenia of childhood (RCC) is the most common subtype of pediatric myelodysplastic syndrome (MDS). RCC is frequently characterized by hypocellular bone marrow (BM), absence of chromosomal aberrations, and low risk of progression to advanced MDS. However, about 10-15% of patients with RCC display an abnormal karyotype with monosomy 7, 7q- or ≥2 aberrations associated with a high risk of progression to MDS with increased blast count. Thus, patients with RCC should be stratified for therapy according to karyotype (see Fig. 1).

Fig. 1: Algorithm for treatment of patients with RCC

In the absence of monosomy 7, 7q- or ≥2 aberrations, RCC patients with mild cytopenia (no transfusion dependency for red blood cells [RBC] and platelets and an absolute neutrophil count [ANC] ≥ 1000/µl) may have a stable course of disease and therefore qualify for a watch-and-wait strategy. For patients with more pronounced cytopenia (transfusion dependency for RBC and/or platelets and/or ANC<1000/µl) treatment is outlined. In patients with hypocellular BM, HSCT with a reduced intensity conditioning (RIC) is the treatment of choice if a matched sibling donor (MSD) is available; in the absence of a MSD options for therapy include HSCT from a matched unrelated donor following RIC, or immunosuppressive therapy (IST) with antithymocyte globuline (ATG) and cyclosporine A (Cs-A). The use of horse ATG is recommended for IST.

In contrast, it is consensus to treat patients with RCC and presence of monosomy 7/
7q- or ≥ 2 chromosomal abnormalities, or normo-/hypercellular BM with HSCT following a myeloablative regimen. HSCT with a regimen consisting of busulfan, cyclophosphamide +/- melphalan has been associated with a negligible risk of relapse, but considerable transplantation related mortality. Therefore, the current EWOG-MDS recommendations include a treosulfan based regimen.

In patients with non-response or relapse after IST, BM aspirate and biopsy should be repeated prior to HSCT and the transplant procedure should be performed according to BM cellularity and karyotype at this time point. Patients who progressed to advanced MDS following IST are to be transplanted according to the recommendations for secondary MDS following severe aplastic anemia (SAA) (see 4).

1.2. RCC patients with hypocellular BM and normal karyotype, unsuccessful karyotype studies, or karyotype other than monosomy 7, 7q- or ≥ 2 aberrations

**Cave:** Irrespective of karyotype, patients with normo- or hypercellular BM are to be treated according to the recommendation for patients with monosomy 7, 7q- or ≥ 2 aberrations.

1.2.1. Investigations to be performed/repeated at time of HSCT within 6 weeks before the allograft

- BM aspirate to evaluate blast percentage
- Karyotype of BM cells to detect abnormalities
- BM trephine to evaluate cellularity, fibrosis and blast infiltration
- Skin biopsy for cryopreservation of cultured fibroblasts
- Cryopreservation of viable BM and peripheral blood (PB) cells
- Storage of DNA

1.2.2. Criteria for donor selection

- HLA-identical sibling BM/PB stem cell (PBSC)/cord blood (CB) donor: serological typing for class I loci (i.e. A, B and C) and high resolution (HR) molecular typing for DRB1 and DQB1 locus if parents typing is available. If not, HR molecular typing for both class I and II loci is recommended
- Phenotypically identical relative: HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 and DQB1 locus
- Unrelated BM/PBSC donor: identical or with a single disparity in class I or II loci with the recipient using HR molecular typing for class I loci (i.e. A, B and C) and for class II loci (i.e. DRB1, DQB1). Preferential choice of DRB1 matched donor is recommended.

1.2.3. Stem cell source

- BM
- PBSC, only if the donor refuses to donate BM
- CB, only for HLA-identical sibling allograft
1.2.4. Graft composition

- Unmanipulated BM cells: > 3.5x10^8 nucleated cells (NC)/kg
- Unmanipulated PBSC: > 4x10^6 CD34+ cells/kg and < 10x10^6 CD34+ cells/kg or < 5x10^7 CD3+ cells/kg
- CB: at least 3.5x10^7 NC/kg before thawing

1.2.5. Conditioning regimen

- ATG Fresenius will be used in patients transplanted from unrelated donors during conditioning regimen for *in vivo* T-cell depletion/modulation: 15 mg/kg/day for 3 consecutive days (-4 to -2). If alternative types of ATG are employed, equivalent doses of the product should be given.
- Preparation will consist of Fludarabine (40 mg/m^2/day from day -8 to day -5) and Thiotepa (5 mg/kg/day from day -4 to day -2).

1.2.6. Strategy for graft-versus-host disease (GVHD) prophylaxis and treatment

- HLA-identical sibling BM/PBSC donor: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) starting from day -1 and with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable), and methotrexate (MTX): 3 doses on days +1, +3 and +6 at a dosage of 10 mg/m^2.
- HLA-identical sibling CB donor: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) with the objective of maintaining serum levels between 100-200 ng/mL. Continuous infusion over 24 hours is also acceptable.
- Unrelated donor recipients: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) starting from day -1 and with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable), and MTX: 3 doses on days +1, +3 and +6 at a dosage of 10 mg/m^2.
- Cs-A tapering should be started around day +100 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place around day + 180.
- Patients with grade II-IV acute GVHD should initially receive systemic steroids at a dosage of 2 mg/kg. If regression occurs, steroids should be slowly tapered and discontinued. For persistent or progressive GVHD second line treatment, according to each centre policy, is recommended.

1.2.7. Monitoring of chimerism/minimal residual disease (MRD)

Monitoring of chimerism through short tandem repeats (STR) is recommended to start at the time of neutrophil recovery and should be performed on day +30, +60, +100 and +180. In case of re-growth of recipient cells, a closer monitoring is recommended in order to obtain information on the evolution of this situation of mixed chimerism. There is no indication for performing donor leukocyte infusion (DLI) in these patients in consideration of the negative risk/benefit ratio of GVHD in these patients.
1.2.8. Special considerations

In patients experiencing either primary or secondary graft failure, a second transplant option should be offered as soon as possible, even considering a T-cell depleted allograft from an HLA-disparate relative if the unrelated volunteer is not willing to donate for the second time. A possible conditioning regimen to be considered is that based on the combination of low-dose cyclophosphamide (300 mg/m²/day from day –6 to day –3), fludarabine (30 mg/m²/day from day –6 to day –3) and single dose total body irradiation (TBI) (2 Gy) plus horse ATG for those given rabbit ATG during the first allograft.

1.3. RCC patients with monosomy 7, 7q- or ≥ 2 aberrations (and any cellularity) and RCC patients with normo- or hypercellular bone marrow (and any karyotype)

1.3.1. Investigations to be performed/repeated at the time of HSCT within 6 weeks before the allograft

- BM aspirate to evaluate blast percentage
- Karyotype of BM cells to detect abnormalities
- BM trephine to evaluate cellularity, fibrosis and blast infiltration
- Skin biopsy for cryopreservation of cultured fibroblasts
- Cryopreservation of BM and PB cells
- Storage of DNA

1.3.2. Criteria for donor selection

- HLA-identical sibling BM/PBSC/CB donor: serological typing for class I loci (i.e. A, B and C) and HR molecular typing for DRB1 and DQB1 locus if parents typing are available. If not, HR molecular typing for both class I and II loci is recommended
- Phenotypically identical relative: HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 and DQB1 locus
- Unrelated BM/PBSC donor: identical or with a single disparity in class I or II loci with the recipient using HR molecular typing for class I loci (i.e. A, B and C) and for class II loci (DRB1, DQB1).
- CB donor: 6/6 or 5/6 matched donor using HR molecular typing for class I loci (i.e. A and B) and DRB1 locus. Preferential choice of DRB1 matched donor is recommended.

1.3.3. Stem cell source

- BM
- PBSC, only if the donor refuses to donate BM
- CB
1.3.4. Graft composition

- Unmanipulated BM cells: > 3.5x10^8 NC/kg
- Unmanipulated PBSC: > 4x10^6 CD34+ cells/kg and < 10x10^6 CD34+ cells/kg or < 5x10^7 CD3+ cells/Kg
- CB: units containing more cells have to be preferentially selected. In any case, a patient must receive at least 3.5x10^7 NC/kg before thawing.

1.3.5. Conditioning regimen

- ATG Fresenius will be used in patients transplanted from unrelated donors or relatives other than an HLA-identical sibling during conditioning regimen for in vivo T-cell depletion/modulation: 15 mg/kg/day for 3 consecutive days (-4 to –2). If alternative types of ATG are employed, equivalent doses of the product should be given.
- Preparation will consist of Thiotepa 8 mg/kg/d on day -7, Treosulfan 14 g/m^2/day for 3 consecutive days (-6 to -4) and Fludarabine 40 mg/m^2/d for 4 consecutive days (-6 to -3).

1.3.6. Strategy for GVHD prophylaxis and treatment

- HLA-identical sibling BM/PBSC donor and patient at HSCT < 12 years: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/Kg/day) starting from day -1 and with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable), HLA-identical sibling BM/PBSC donor and patient at HSCT ≥ 12 years: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) and short course MTX (3 doses on days +1, +3 and +6 at a dosage of 10 mg/m^2).
- Cs-A tapering should be started around day +60 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place around day + 100.
- HLA-identical sibling CB donor: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/Kg/day) with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable).
- Unrelated BM/PBSC donor recipients: Cs-A 1.5 mg/Kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) starting from day –1 and with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable), and MTX: 3 doses on days +1, +3 and +6 at a dosage of 10 mg/m^2.
- Unrelated CB donor recipients: the recommended GVHD prophylaxis is Cs-A (at the same dose indicated for BM/PBSC allografts), and steroids (methylprednisolone 1.5 mg/kg/day starting from day -4 for 3 weeks with a rapid tapering in the absence of GVHD in 2 more weeks). Alternatively, steroids can be replaced by mycophenolatmofetil (MMF).
- Cs-A tapering should be started around day +100 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place around day +140.
- Patients with grade II-IV acute GVHD should initially receive systemic steroids at a dosage of 2 mg/kg. If regression occurs, steroids should be slowly...
tapered and discontinued. For persistent or progressive GVHD second line treatment, according to each centre policy, is recommended.

2. Primary advanced MDS: RAEB, RAEB-t and MDR-AML

2.1. Introduction
Patients with advanced MDS including refractory anemia with excess blasts (RAEB), RAEB in transformation (RAEB-T) or acute myeloid leukemia (AML) evolving from MDS (MDR-AML) have a poor prognosis. Conventional AML-type chemotherapy without HSCT resulted in survival rates below 30% and all patients need to be transplanted. Previous analysis from the EWOG-MDS study showed that the overall survival rate at 5 years of 97 patients with advanced MDS, who received HSCT with the conditioning regimen of busulfan, cyclophosphamide, and melphalan, was 63%\(^5\). The subtype of MDR-AML is related with inferior outcome. Because patients with the age of \(\geq12\) years had a high risk of transplantation-related mortality in this study, we recommend treosulfan based conditioning regimen in this age group. The presence of a structurally complex karyotype is a strong prognostic marker predicting poor outcome\(^6\).

2.2. Investigations to be performed/repeated at time of HSCT within 6 weeks before the allograft
- BM aspirate to evaluate blast percentage
- Karyotype of BM cells to detect abnormalities
- BM trephine to evaluate cellularity, fibrosis and blast infiltration
- Skin biopsy for cryopreservation of cultured fibroblasts
- Cryopreservation of viable BM and PB cells
- Storage of DNA

2.3. Criteria for donor selection
- HLA-identical sibling BM/PBSC/CB donor: serological typing for class I loci (i.e. A, B and C) and HR molecular typing for DRB1 locus if parents typing available. If not, HR molecular typing for both class I and II loci is recommended
- Phenotypically identical relative: HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 locus
- Unrelated BM/PBSC donor: identical or with a single disparity in class I or II loci with the recipient using HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 locus
- CB donor: 6/6 or 5/6 matched donor using HR molecular typing for class I loci (i.e. A and B) and DRB1 locus. Preferential choice of DRB1 matched donor is recommended
2.4. Stem cell source

- BM
- PBSC
- CB

2.5. Graft composition

- Unmanipulated BM cells: > $3.5 \times 10^8$ NC/kg
- Unmanipulated PBSC: > $4 \times 10^6$ CD34+ cells/kg and < $10 \times 10^6$ CD34+ cells/kg or < $5 \times 10^7$ CD3+ cells/kg
- CB: units containing more cells have to be preferentially selected. In any case, a patient must receive at least $3.5 \times 10^7$ NC/kg before thawing.

2.6. Conditioning regimen for patients < 12 yrs at the time of HSCT

- ATG Fresenius will be used in patients transplanted from unrelated donors or relatives other than an HLA-identical sibling during conditioning regimen for in vivo T-cell depletion/modulation: 10 mg/Kg/day for 3 consecutive days (-4 to – 2). If alternative types of ATG are employed, equivalent doses of the product should be given.
- Preparation will consist of busulfan i.v. in 4 doses per day for 4 consecutive days (-7 to -4) (according to the manufacturers recommendation 0.8 - 1.2 mg/kg/dose) (or orally when the i.v. preparation is not available), cyclophosphamide 60 mg/kg/d on 2 consecutive days (-3 to -2) and melphalan 140 mg/m$^2$/d on day -1.
- Busulfan i.v. with an adjustment of the dose according to recipients BW is recommended. PK study on the first dose of busulfan (especially if administered orally) is recommended and plasmatic levels of the drug should be comprised in the range between 700 - 950 ng/ml.

2.7. Conditioning regimen for patients ≥ 12 yrs at the time of HSCT

- ATG Fresenius will be used in patients transplanted from unrelated donors or relatives other than an HLA-identical sibling during conditioning regimen for in vivo T-cell depletion/modulation: 10 mg/Kg/day for 3 consecutive days (-4 to – 2). If alternative types of ATG are employed, equivalent doses of the product should be given.
- Preparation will consist of Thiotepa 8 mg/kg/d on day -7, Treosulfan 14 g/m2/d for 3 consecutive days (-6 to -4) and Fludarabine 40 mg/m2/d for 4 consecutive days (-6 to -3).

2.8. Discussion on strategy for GVHD prophylaxis and treatment

HLA-identical sibling BM/PBSC donor and patient at HSCT < 12 years Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) starting from day –1 and with the objective of maintaining serum levels between 100-200 ng/mL(continuous infusion over 24 hours is also acceptable); HLA-identical sibling BM/PBSC donor and patient at HSCT ≥ 12 years Cs-A1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) and short course MTX (3
doses on days +1, +3 and +6 at a dosage of 10 mg/m$^2$).

- Cs-A tapering should be started around day +60 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place around day + 100.
- HLA-identical sibling CB donor: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) with the objective of maintaining serum levels between 100-200 ng/mL (continuous infusion over 24 hours is also acceptable);
- Unrelated BM/PBSC donor: Cs-A 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) and short course MTX (3 doses on days +1, +3 and +6 at a dosage of 10 mg/m$^2$).
- Unrelated CB donor recipients: the recommended GVHD prophylaxis is Cs-A (at the same dose indicated for BM/PBSC allografts) plus steroids (methylprednisolone 1.5 mg/kg/day starting from day - 4 for 3 weeks with a rapid tapering in the absence of GVHD in 2 more weeks). Alternatively, steroids can be replaced by MMF.
- Cs-A tapering should be started around day +100 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place around day + 140.
- Patients with grade II-IV acute GVHD should initially receive systemic steroids at a dosage of 2 mg/kg. If regression occurs, steroids should be slowly tapered and discontinued. For persistent or progressive GVHD second line treatment, according to each centre policy, is recommended.

2.9. Special considerations

The role of intensive chemotherapy prior to HSCT has been a matter of debate for decades and there are no solid data to make clear evidence based recommendations. However, patients with MDR-AML may have a benefit from AML like therapy prior to HSCT as reflected by a tendency for a better event free survival (EFS). Furthermore, our recent analysis of the 159 patient with advanced MDS showed that patients with more than 20% blasts at HSCT have a significantly worse probability of event-free survival due to a slightly higher rate of TRM and a significantly higher risk of relapse. Based on these observations patients with advanced disease (≥ 20% BM blasts) are eligible to receive chemotherapy prior to HSCT. It is not possible to clearly define the best type of intensive chemotherapy and the pre-transplant regimen has to be adapted to the individual case. However, there is an overall agreement that patients with MDR-AML should currently be treated with one cycle of cytoreductive chemotherapy with the aim of reducing blast count (not an induction of remission) and then be transplanted. It is proposed to base the pre-transplant cytoreductive chemotherapy on the international AML-Relapse protocol from 2002 (using eg. daunoxome /fludarabin). There is currently no consensus on the use of cytoreductive therapy in patients with RAEB-t (≥20, <30% BM blasts) and application of chemotherapy should be based on an individual decision taking the clinical condition, the rate of progression and the karyotype into account.
3. Secondary MDS following treatment for a first malignancy

Patients with secondary MDS following chemotherapy +/- radiation have a poor prognosis. Preliminary results of the EWOG MDS study showed that the outcome of patients with secondary MDS following haematological malignancies was superior compared to patients with secondary MDS following solid tumors. In addition, a structural complex karyotype was associated with very poor prognosis. In patients with less than 5% of blasts in BM and/or PB, all treatment failures were associated with transplant related complications and no relapse was observed in this group. Based on these observations it is recommended to treat patients with secondary MDS and less than 5% of blast in BM and/or PB with the Thiotepa/Treosulfan/Fludarabine regimen described for patients with RCC and monosomy 7, 7q- or ≥ 2 abnormalities (see 1.3). Patients with secondary MDS and an increase in blasts following haematological malignancies should be transplanted according to the recommendations for advanced MDS (see 2). Based on the current data it is not possible to give clear recommendations for 2nd MDS after solid tumour or with complex karyotype.

4. Secondary MDS following SAA

Outcome of patients with secondary MDS following IST for SAA is unfavourable. The major problem after HSCT in these patients is the high rate of TRM. It is recommended to transplant patients with 2nd MDS after SAA without increase of blasts according to the recommendations for RCC and monosomy 7, 7q- or ≥ 2 abnormalities (Thiotepa/Treosulfan/Fludarabine) (see 1.3), whereas patients with an increase in blasts should be treated according to the recommendations for primary advanced MDS (see 2).

5. Juvenile myelomonocytic leukemia (JMML)

5.1. Introduction

The curative treatment for patients with JMML is HSCT and the EWOG-MDS group has successfully used a busulfan-based regimen in this cohort of patients. However, the clinical course and the outcome of HSCT in patients with JMML are variable and at least partially depend on the molecular genotype. Patients with germline CBL and germline PTPN11 mutations showed no difference in survival with or without HSCT. Therefore, for these particular there is no clear indication to HSCT. However, they may benefit from cytoreduction (i.e. 6-mercaptopurine: 6-MP) and the indication for this therapy should be guided by a close clinical observation.

In contrast, patients with JMML and NF1, PTPN11 mutation (somatic), KRAS mutation (somatic) and without known molecular lesion have no chance of survival without HSCT and, thus, for them, there is an indication for HSCT. Patients with NRAS mutation (somatic) show various clinical courses and some patients survive without HSCT. In these patients decision to proceed with HSCT should be made depending on the severity of disease.
5.2. Investigations to be performed/repeated at time of HSCT, that is within 6 weeks before the allograft

- BM aspirate to evaluate blast percentage
- Karyotype of BM cells to detect abnormalities
- BM trephine to evaluate cellularity, fibrosis and blast infiltration
- Skin biopsy for cryopreservation of cultured fibroblasts
- Cryopreservation of viable BM and PB cells
- Storage of DNA

5.3. Criteria for donor selection

- HLA-identical sibling BM/PBSC/CB donor: serological typing for class I loci (i.e. A, B and C) and HR molecular typing for DRB1 locus if parents typing available. If not, HR molecular typing for both class I and II loci is recommended
- Phenotypically identical relative: HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 locus;
- Unrelated BM/PBSC donor: identical or with a single disparity in class I or II loci with the recipient using HR molecular typing for class I loci (i.e. A, B and C) and for DRB1 locus.
- CB donor: 6/6 or 5/6 matched donor using HR molecular typing for class I loci (i.e. A and B) and DRB1 locus. Preferential choice of DRB1 matched donor is recommended.

5.4. Stem cell source

- BM
- PBSC
- CB

5.5. Graft composition

- Unmanipulated BM cells: > 3.5x10^8 NC/kg
- Unmanipulated PBSC: > 4x10^5 CD34+ cells/kg and < 10x10^6 CD34+ cells/kg or < 5x10^7 CD3+ cells/kg
- CB: units containing more cells have to be preferentially selected. In any case, a patient must receive at least 3.5 x10^7 NC/kg before thawing.

5.6. Conditioning regimen

- ATG Fresenius will be used in patients transplanted from unrelated donors or relatives other than an HLA-identical sibling during conditioning regimen for in vivo T-cell depletion/modulation: 10 mg/kg/day for 3 consecutive days (-4 to – 2). If alternative types of ATG are employed, equivalent doses of the product should be given.
- Preparation will consist of busulfan i.v. in 4 doses per day for 4 consecutive days (-7 to -4) (according to the manufacturers recommendation 0.8 - 1.2 mg/kg/dose) (or orally when the i.v. preparation is not available),
cyclophosphamide 60 mg/kg/day on 2 consecutive days (-3 to -2) and melphalan 140 mg/m²/d on day -1.

- Busulfan i.v. with an adjustment of the dose according to recipients BW is recommended. PK study on the first dose of busulfan (especially if administered orally) is recommended and plasmatic levels of the drug should be comprised in the range between 700 - 950 ng/ml.

5.7. Strategy for GVHD prophylaxis and treatment

- HLA-identical sibling BM/CB/PBSC donor and patient at HSCT younger than 4 years and with less than 20% BM blasts: Cs-A 1 mg/kg in 2-hour infusion twice a day (total dose 2 mg/kg/day) starting from day −1 and with the objective of maintaining serum levels between 80-150 ng/mL
- HLA-identical sibling BM/CB/PBSC donor and patient at HSCT older than 4 years or with more than 20% BM blasts: Cs-A 0.5 mg/kg in 2-hour infusion twice a day (total dose 1 mg/kg/day)
- Unrelated donor recipients or children transplanted from a relative other than an HLA-identical sibling: Cs-A 1 mg/kg in 2-hour infusion twice a day (total dose 2 mg/kg/day) starting from day −1 and with the objective of maintaining serum levels between 80-150 ng/mL
- Unrelated BM/PBSC donor recipients or children transplanted from a relative other than an HLA-identical sibling will receive MTX: 3 doses on days +1, +3 and +6 at a dosage of 10 mg/m²
- For children given an unrelated donor CBT, the recommended GVHD prophylaxis is Cs-A (at the same dose indicated for BM/PBSC allografts) plus steroids (methylprednisolone 1.5 mg/Kg/day starting from day −4 for 3 weeks with a rapid tapering in the absence of GVHD in 2 more weeks). Alternatively, steroids can be replaced by MMF.
- Cs-A tapering should be started around day +40 in the absence of grade II-IV acute GVHD and steroid treatment. Cs-A discontinuation should take place between day + 60 and +90.
- Patients with grade I (namely only limited skin involvement) acute GVHD should not receive systemic steroid treatment.
- Patients with grade II-IV should initially receive systemic steroids at a dosage of 2 mg/kg. If regression occurs steroids should be rapidly tapered and discontinued (e.g. within 2 weeks). For persistent or progressive GVHD second line treatment, according to each center’s policy, is recommended.

5.8. Monitoring of chimerism/MRD

Monitoring of chimerism through STR or SNP-STR should start on day +15 after the allograft and it is recommended to be performed weekly on PB until day +90 and then at least monthly until the patient is off immune-suppressive therapy. In case of re-growth of recipient cells (e.g. first positivity of mixed chimerism or reappearance of MRD) immune-suppressive therapy must be discontinued immediately. There is no indication for performing DLI in these patients.
5.9. Special considerations

In case of progression to frank relapse or if the patient experiencing mixed chimerism is not receiving any immune suppressive therapy a second HSCT must be early considered. Preliminary data demonstrate promising results for 2nd HSCT in patients with relapsed JMML using the previously described thiotepa/treosulfan/fludarabine regimen and, thus, the use of this regimen is recommended.

References


