Received: 17 January 2024 | Accepted: 21 May 2024

DOI: 10.1002/hem3.120

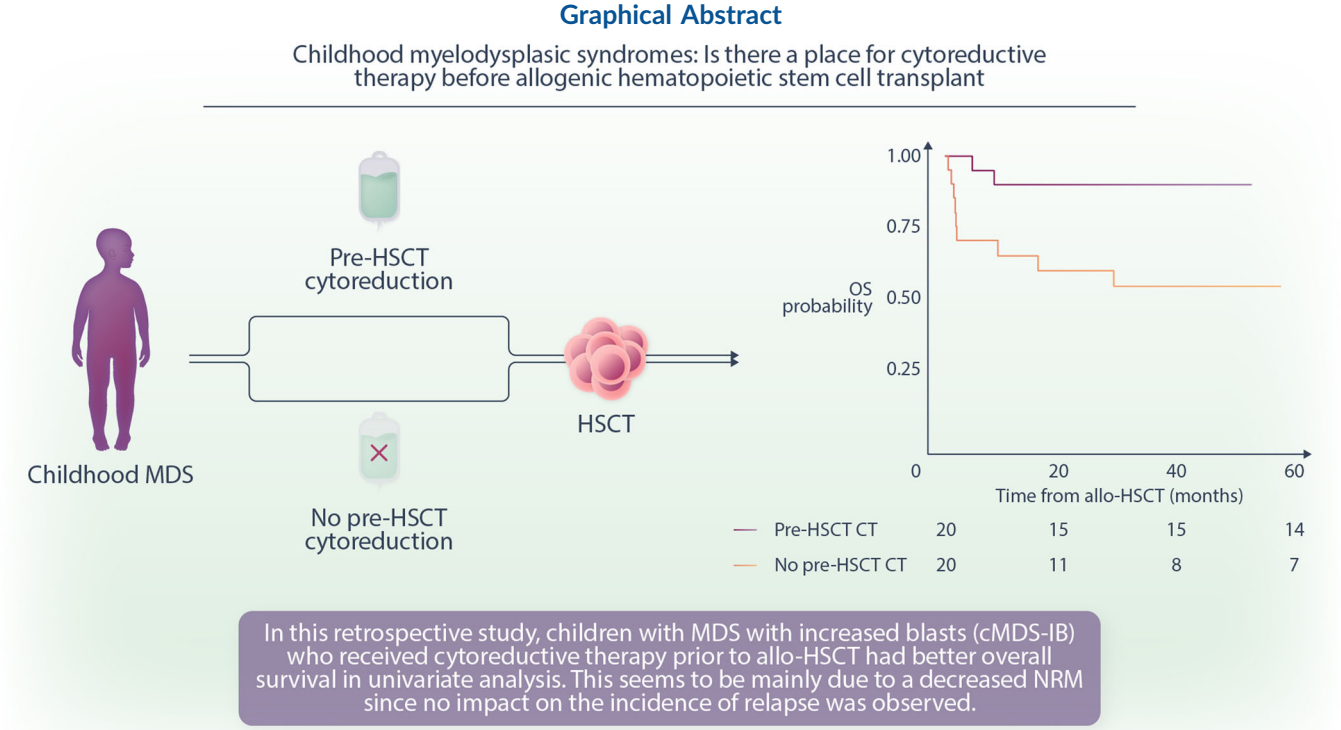
HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

ARTICLE

Childhood myelodysplastic syndromes: Is cytoreductive therapy useful before allogeneic hematopoietic stem cell transplantation?

Baptiste Le Calvez[1,2] | Maxime Jullien[3] | Jean H. Dalle[4] | Cécile Renard[5] | Charlotte Jubert[6,7] | Arthur Sterin[8] | Catherine Paillard[9] | Anne Huynh[10] | Sarah Guenounou[10] | Bénédicte Bruno[11] | Virginie Gandemer[12] | Nimrod Buchbinder[13] | Pauline Simon[14] | Cécile Pochon[15] | Anne Sirvent[16] | Dominique Plantaz[17] | Justyna Kanold[18] | Marie C. Béné[2,19] | Fanny Rialland[1,20] | Audrey Grain[1,2,20] | on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

Graphical Abstract



Received: 17 January 2024 | Accepted: 21 May 2024

DOI: 10.1002/hem3.120

ARTICLE

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

Childhood myelodysplastic syndromes: Is cytoreductive therapy useful before allogeneic hematopoietic stem cell transplantation?

Baptiste Le Calvez[1,2] | Maxime Jullien[3] | Jean H. Dalle[4] | Cécile Renard[5] | Charlotte Jubert[6,7] | Arthur Sterin[8] | Catherine Paillard[9] | Anne Huynh[10] | Sarah Guenounou[10] | Bénédicte Bruno[11] | Virginie Gandemer[12] | Nimrod Buchbinder[13] | Pauline Simon[14] | Cécile Pochon[15] | Anne Sirvent[16] | Dominique Plantaz[17] | Justyna Kanold[18] | Marie C. Béné[2,19] | Fanny Rialland[1,20] | Audrey Grain[1,2,20] | on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

Correspondence: Baptiste Le Calvez (Baptiste.lecalvez@chu-nantes.fr)

Abstract

For most patients with childhood myelodysplastic syndrome (cMDS), allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative option. In the case of increased blasts (cMDS-IB), the benefit of pretransplant cytoreductive therapy remains controversial. In this multicenter retrospective study, the outcomes of all French children who underwent allo-HSCT for cMDS reported in the SFGM-TC registry between 2000 and 2020 were analyzed ($n = 84$). The median age at transplantation was 10.2 years. HSCT was performed from matched sibling donors (MSD) in 29% of the cases, matched unrelated donors (MUD) in 44%, haploidentical in 6%, and cord blood in 21%. Myeloablative conditioning was used in 91% of cases. Forty-eight percent of patients presented with cMDS-IB at diagnosis (median BM blasts: 8%). Among them, 50% received pretransplant cytoreductive therapy. Five-year overall survival (OS), cumulative incidence of nonrelapse mortality (NRM), and relapse were 67%, 26%, and 12%, respectively. Six-month cumulative incidence of grade II–IV acute graft-versus-host disease was 46%. Considering the whole cohort, age under 12, busulfan/cyclophosphamide/melphalan conditioning or MUD were associated with poorer 5-year OS. In the cMDS-IB subgroup, pretransplant cytoreductive therapy was associated with a better OS in univariate analysis. This seems to be mainly due to a decreased NRM since no impact on the incidence of relapse was observed. Overall, those data may argue in favor of cytoreduction for cMDS-IB. They need to be confirmed on a larger scale and prospectively.

[1]Department of Pediatric Hematology, CHU Hôtel Dieu, Nantes, France
[2]CRCI2NA, INSERM U1307, CNRS, Université d'Angers/Université de Nantes, France
[3]Department of Clinical Hematology, CHU Hôtel Dieu, Nantes, France
[4]Department of Pediatric Hematology, Robert Debré Hospital, GHU APHPNOrd–Université Paris Cité, Paris, France
[5]Department of Pediatric Hematology, IHOPe, HCL Lyon, Lyon, France
[6]Department of Pediatric Hematology Oncology, F-33000 Bordeaux, Bordeaux, France
[7]Department of Pediatric Hematology, CHU de Bordeaux, Bordeaux, France
[8]Department of Pediatric Hematology, La Timone APHM, Marseille, France
[9]Department of Pediatric Hematology, Strasbourg, France
[10]Department of Hematology, CHU/IUCT Oncopole Toulouse, Toulouse, France
[11]Department of Pediatric Hematology, Hôpital Jeanne de Flandre, CHRU Lille, Lille, France
[12]Department of Pediatric OncoHematology, Rennes University Hospital, University of Rennes, Rennes, France
[13]Department of Pediatric Hematology, Hopital Charles Nicolle CHU Rouen, Tunis, Tunisia
[14]Department of Pediatric Hematology, CHRU de Besancon, Besancon, France
[15]Department of Pediatric Hematology, CHRU de Nancy, Nancy, France

INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells characterized by the presence of persistent cytopenias, resulting from ineffective hematopoiesis, and by a high risk of transformation to acute myeloblastic leukemia (AML). Childhood MDS (cMDS) are rare entities with a specific genomic landscape. Inherited predispositions (BM failure, germline mutations) are currently identified in about 15% of cases.[1–7]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative option for this condition and is recommended in case of excess blasts, unfavorable karyotype (monosomy 7, complex karyotype), transfusion dependency, or persistent neutropenia.[2]

For cMDS without excess blasts (cMDS-LB), allo-HSCT after busulfan-cyclophosphamide-based myeloablative conditioning regimens (MAC) provided an overall survival (OS) of about 75%, nonrelapse mortality (NRM) being the major cause of treatment failure.[8] More recently, reduced-intensity conditioning regimens (RIC) have provided better results in selected patients with non-high-risk cytogenetics and BM hypoplasia.[2,9]

For cMDS with increased blasts (cMDS-IB), intensive chemotherapy alone has yielded disappointing results and allo-HSCT appears to be the treatment of choice.[10,11] In this setting, the EWOG-MDS 98 study showed a 5-year OS at 63% after allo-HSCT following MAC conditioning (busulfan, cyclophosphamide, and melphalan [BuCyMel]).[12] In this study, NRM and relapse accounted for an equivalent proportion of mortality (21% each).

One of the most controversial issues in the treatment of cMDS-IB is the impact of cytoreductive therapy prior to allo-HSCT. In the EWOG-MDS 98 study, cytoreductive intensive chemotherapy prior to allo-HSCT did not improve OS or event-free survival (EFS) for cMDS.[12] There was no difference in the incidence of relapse between patients who had or had not received cytoreductive therapy prior to HSCT. However, subgroup analysis of patients with MDS-related AML demonstrated a significant decrease in relapse incidence in the cytoreductive chemotherapy group, even though a blast count below 20% at the time of transplant had no impact on event-free survival (EFS) or relapse incidence in this cohort. A recent Japanese series also found no advantage to pretransplant cytoreductive chemotherapy in 242 children.[13] In univariate analysis, cytoreductive therapy was associated with a lower OS, but this was not confirmed in multivariable analysis. There was no difference in the incidence of relapse between patients who received cytoreductive therapy and those who did not.

To assess factors influencing the outcome of allo-HSCT in cMDS and notably the role of pretransplant cytoreductive therapy the outcomes of French pediatric patients were examined here from data of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC).

MATERIALS AND METHODS

Eligibility criteria and study design

This multicenter retrospective study included all pediatric patients (≤18 years old) reported to the SFGM-TC registry who underwent an allo-HSCT for a cMDS between January 2000 and January 2020 in France. Patients with acute leukemia (≥20% bone marrow blasts at diagnosis) or juvenile myelomonocytic leukemia were excluded. Data were obtained through the ProMISe database (the internet-based system shared by all European transplantation centers). Medical records of the patients included were reviewed to collect missing data and update follow-up. All patients or their legal representatives provided signed consent for inclusion in the registry and the collection and use of anonymized medical data. Approval was obtained from the institutional review board of each institution. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analyses

The endpoints examined in this study were 5-year OS, PFS, NRM, graft versus host disease (GvHD)-free/relapse-free survival (GRFS), and cumulative incidence of relapse (CIR). OS was defined as the time from the day of allo-HSCT to death or last follow-up. Relapse was defined as any event related to the re-occurrence of the disease. PFS was defined as the time from allo-HSCT to death or relapse. NRM was defined as death from any cause without previous relapse or disease progression. GRFS was defined as survival without grade III–IV aGvHD, extensive cGvHD, or disease relapse.[14] aGvHD and cGvHD were diagnosed and graded according to standard criteria.[15,16] OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cumulative incidence was employed to calculate NRM, CIR, aGvHD, and cGvHD, considering the presence of competing risks.[17] In this context, NRM and relapse were analyzed as competing events. Death or relapse were considered as competing events for aGvHD and cGvHD incidence estimation. Survival probabilities are presented as percentages and 95% confidence intervals (95% CI).

Univariate and multivariable analyses were carried out using the Cox proportional-hazard model for OS, PFS, and GRFS, and using cumulative risk regression for NRM, CIR, and GvHD.

Factors considered for univariate analysis were: gender, WHO 2022 category,[18] age, presence of germline predisposition, therapy-related MDS status, high-risk cytogenetic abnormalities (monosomy 7, complex karyotype), pretransplant cytoreductive therapy, BM blast percentage at diagnosis, BM blast percentage at transplantation, year of allo-HSCT, time from diagnosis to transplantation, conditioning regimen, donor-related data (gender, age, HLA-matching), and graft source. Of note, all UCB recipients were pooled for analyses regardless of HLA-matching since this data was not fully captured in the registry. Factors with a $p < 0.10$ in univariate analysis or of interest for the study were included in multivariable analysis.

All tests were two-sided and $p < 0.05$ were considered statistically significant. Analyses were performed using R software, version 4.2.2 (The R Foundation for Statistical Computing).

RESULTS

Patient characteristics

The cohort included 84 pediatric patients with cMDS from 17 French centers, allografted between 2000 and 2020. Patient characteristics and allo-HSCT procedures are described in Table 1. The median age at

[16]Department of Pediatric Hematology, CHU de Montpellier, Montpellier, France
[17]Department of Pediatric Hematology CHU Grenoble Alpes, Grenoble, La Tronche, France
[18]Department of Pediatric Hematology, CHU de Clermont Ferrand, Clermont-Ferrand, France
[19]Faculty of Medicine, Nantes University, Nantes, France
[20]CICFEA, CHU de Nantes, Nantes, France

TABLE 1 Patients, disease, and transplant characteristics.

	n = 84
Age (IQR)	10.2 (7.2, 14.2)
Sex, *n* (%)	
Female	43 (51%)
Male	41 (49%)
WHO 2022, *n* (%)	
MDS with increased blasts (MDS-IB)	40 (48%)
MDS with low blasts (MDS-LB)	44 (52%)
Germline predisposition, *n* (%)	20 (24%)
Therapy-related MDS, *n* (%)	15 (20%)
Missing data	10
Cytogenetics, *n* (%)	
Normal	15 (18%)
Monosomy 7	54 (64%)
Complex karyotype	6 (7.1%)
Missing data	9 (11%)
Pre-HSCT cytoreductive therapy, *n* (%)	24 (29%)
Pre-HSCT chemotherapy, *n* (%)	20 (25%)
Missing data	5
Bone marrow blasts at diagnosis median (range)	5.0% (0.0–9.0)
Missing data	5
Bone marrow blasts at the time of HSCT median (range)	3.0% (0.0–5.0)
Missing data	14
Year of HSCT median (range)	2012 (2000–2020)
Time from diagnosis to HSCT median (range)	184 (113–353)
Number of HSCT, *n* (%)	
First	75 (89%)
Second	9 (11%)
Donor type, *n* (%)	
MSD	24 (29%)
MUD	37 (44%)
UCB	18 (21%)
Haploidentical	5 (6%)
Conditioning regimen, *n* (%)	
BuCy	47 (58%)
BuCyMel	9 (11%)
Flu-based	21 (26%)
TBI-based	4 (4.9%)
Missing data	3
ATG, *n* (%)	32 (38%)
GvHD prophylaxis, *n* (%)	
CSA	29 (35%)
CSA and steroid	13 (16%)
CSA and MMF	11 (13%)
CSA and MTX	20 (24%)
CSA MTX and corticosteroids	1 (1.2%)
CSA MTX and MMF	1 (1.2%)
CSA and PTCy	2 (2.4%)
CSA, MMF, and PTCy	5 (6.1%)
Missing data	2
Graft source, *n* (%)	
BM	57 (68%)
UCB	18 (21%)
PBSC	9 (11%)

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; Bu, busulfan; CSA, ciclosporin A; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; Mel, melphalan; MMF, mycophenolate mofetil; MSD, matched sibling donor; MTX, methotrexate; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; PTCy, posttransplant cyclophosphamide; TBI, total body irradiation; UCB, umbilical cord blood.

transplant was 10.2 years (interquartile range [IQR]: 7.2–14.2). Fifteen patients (20%) had therapy-related MDS. Germline predispositions were identified in 24% of patients, mostly *GATA 2* (40%), p53 (15%), *PTPN11* (5%), and *MPL* mutations (5%). Hematologic cytogenetic abnormalities were detected for 82% of the patients, including 64% of monosomy 7. Forty-eight percent of the patients presented with increased blasts at diagnosis (MDS-IB). Twenty-nine percent of patients received a pretransplant cytoreductive therapy, which consisted of AML-like intensive chemotherapy in 83% of the cases. Four patients received azacitidine. No patient received venetoclax.

Myeloablative conditioning regimens were used in most cases (91%), with busulfan/cyclophosphamide and fludarabine-based regimens for 58% and 26% of the patients, respectively. Allo-HSCT was performed from matched sibling donors (MSD) in 29% of the cases, matched unrelated donors (MUD) in 44%, and haploidentical-related donors in 6%. The stem-cell source was BM in 68% of the cases. Umbilical cord blood (UCB) was used in 21% of cases.

Main results of the overall population

Considering the whole cohort, 5-year OS and PFS were 67% (95% CI: 57%–78%) and 63% (95% CI: 54%–74%), respectively (Figure 1). Five-year NRM and CIR were 26% (95% CI:17%–35%) and 12% (95% CI: 5.6%–20%), respectively (Figure 1). Six-month cumulative incidences of grade II–IV and III–IV aGvHD were 46% (95% CI: 35%–57%) and 25% (95% CI: 16%–35%), respectively. Five-year cumulative incidences of cGvHD and extensive cGvHD were 23% (95% CI: 13%–42%) and 13% (95% CI: 6.5%–22%), respectively.

Transplant-related toxicity resulted in the death of 21 patients, 15 of them from GvHD. There was no significant difference between patients who died of GvHD and those who died of other causes in terms of age at transplantation, cytoreductive therapy prior to transplantation, conditioning regimen, donor source, or GvHD prophylaxis. Only the BM blast count at transplantation was significantly higher in patients who died of GvHD ($p = 0.007$).

Analysis of factors associated with posttransplant outcomes in the overall population

The main factors associated with OS, PFS, NRM, GRFS, grade III–IV aGVHD, and cGVHD in the multivariable analysis are shown in Figure 2 and Supporting Information S1: Table S1 and Supporting Information S1: Figure S1.

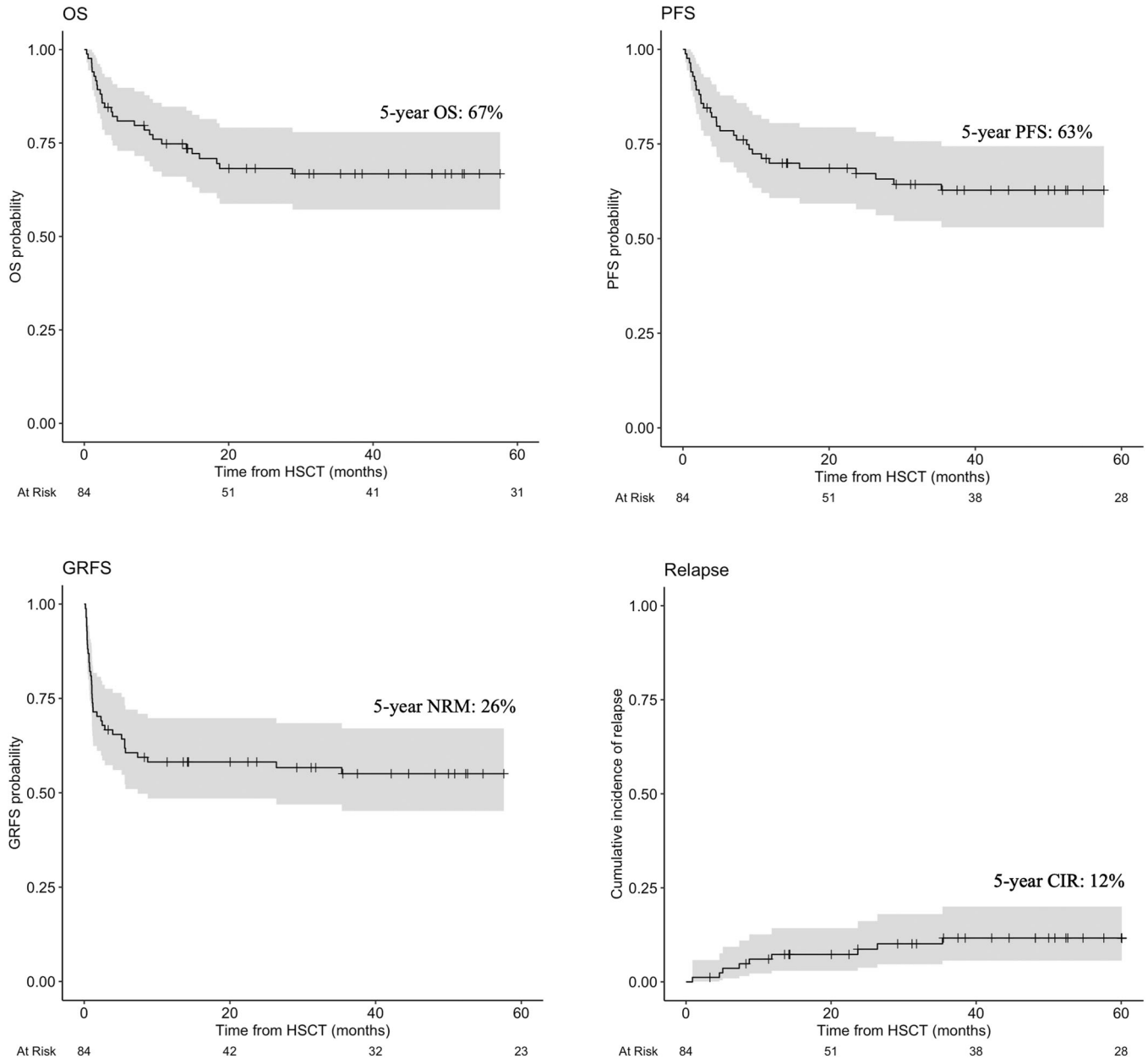


FIGURE 1 Overall (OS), progression-free (PFS), relapse-free/GVHD-free (GRFS) survival, and cumulative incidence of relapse (CIR) in the whole cohort. HSCT, hematopoietic stem cell transplantation.

Approximately a third of the cohort received pretransplant cytoreductive therapy (24/84). Patients who received a pretransplant cytoreductive therapy were more likely to be female ($p = 0.023$), and to have excess blasts at diagnosis (83% of the cases, $p < 0.001$), compared with untreated patients. Of the 24 treated patients, 16 (67%) achieved complete cytological remission. In multivariable analysis, having received a pretransplant cytoreductive therapy was not associated with a significant benefit in terms of OS (Figure 3A), PFS, NRM, CIR, or GRFS. The presence of blasts excess at transplant (cut-off 5%) did not appear to influence OS, PFS, NRM, and CIR in the whole population.

In multivariable analysis, OS (HR: 0.91, 95% CI: 0.84–0.98, $p = 0.015$), PFS (HR: 0.89, 95% CI: 0.82–0.97, $p = 0.007$) and GRFS (HR: 0.92, 95% CI: 0.86–0.99, $p = 0.022$) improved over the years (Supporting Information S1: Figure S1), while NRM decreased significantly in univariate analysis (HR: 0.90, 95% CI: 0.83–0.97, $p = 0.004$). This was not confirmed in multivariable analysis (HR: 0.89, 95% CI: 0.80–1.00, $p = 0.053$).

Age under 12 years was associated with a lower OS (HR: 0.36, 95% CI: 0.13–0.98, $p = 0.046$) (Supporting Information S1: Figure S1) and higher incidence of grade III–IV aGvHD (HR: 0.11, 95% CI: 0.02–0.48, $p = 0.003$) in multivariable analysis. There was no difference between patients under 12 years of age and the older ones, notably in terms of germline predisposition, excess blasts at diagnosis or transplantation, cytogenetics, year of transplantation, donor HLA compatibility, conditioning regimen, or GvHD prophylaxis.

Compared with the BuCy conditioning regimen, BuCyMel was associated with a lower probability of OS (HR: 3.22, 95% CI:

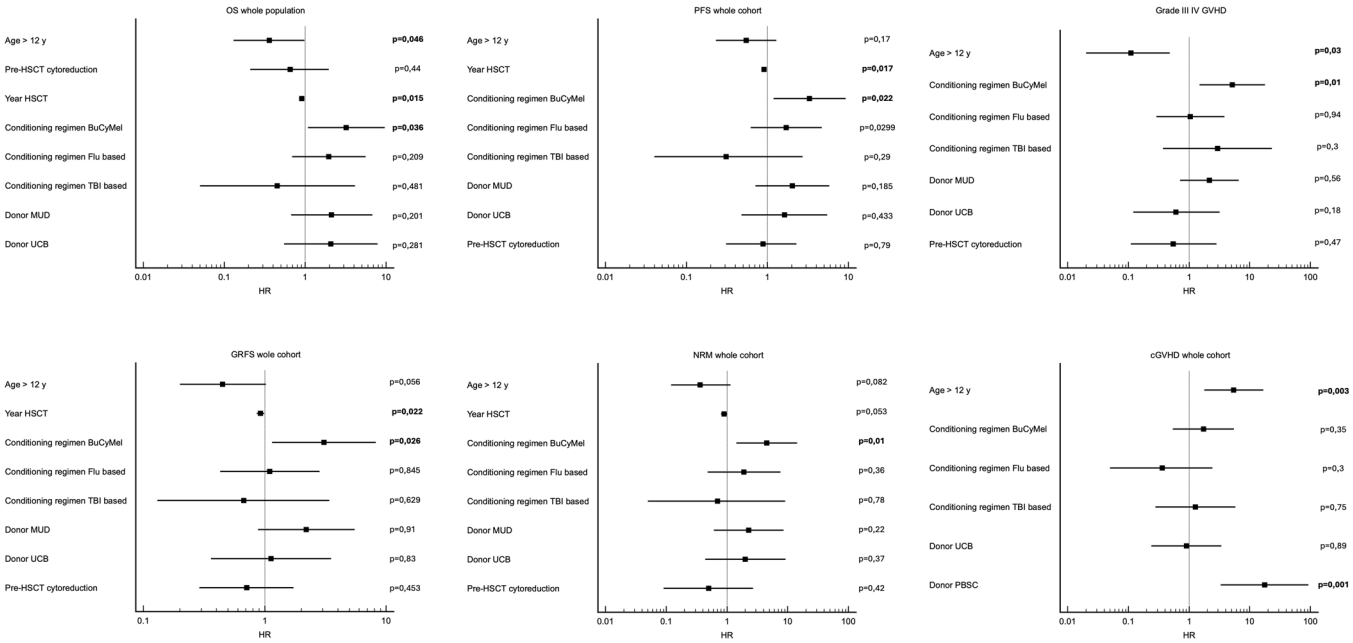


FIGURE 2 Forest plot. Multivariable analysis of factors influencing overall survival (OS), progression-free survival (PFS), grade III–IV acute graft versus host disease (GVHD), GVHD-free/relapse-free survival (GRFS), nonrelapse mortality (NRM), and chronic GVHD (cGVHD) in the global cohort. The conditioning regimens are compared to BuCy. Donors are compared to MSD. Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; Mel, melphalan; MSD, match sibling donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cell; UCB, umbilical cord blood.

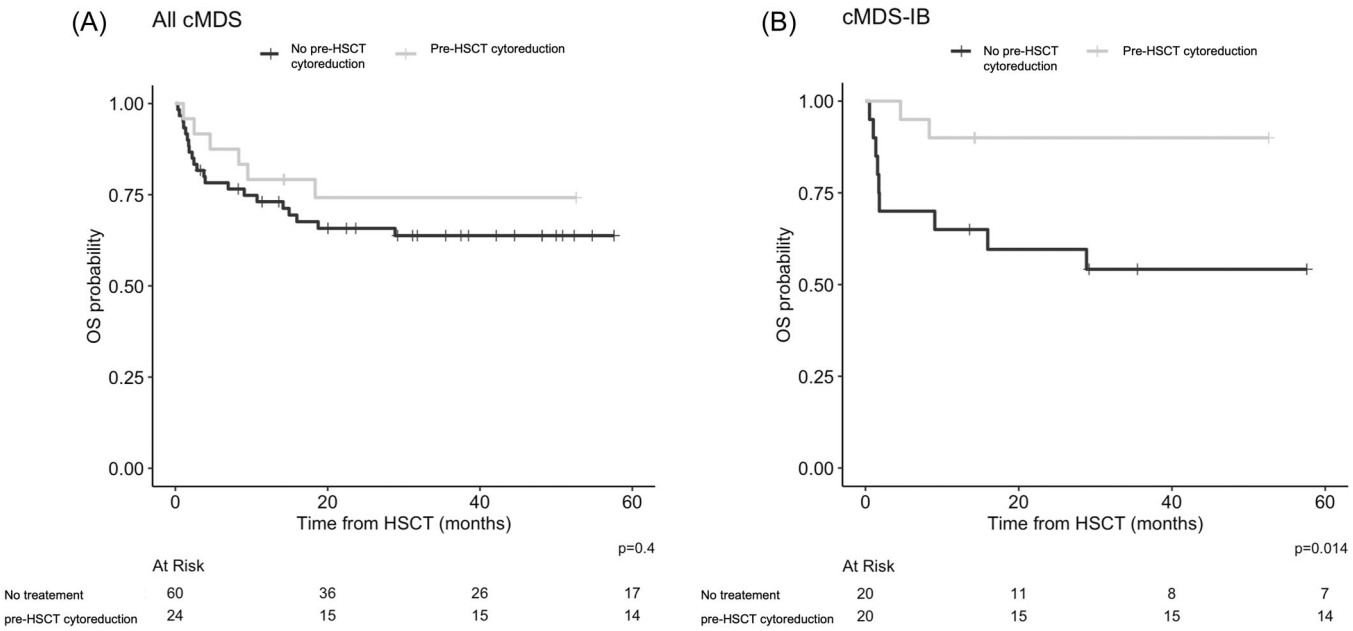


FIGURE 3 Overall survival (OS) according to pretransplant (HSCT) cytoreductive therapy (CT). Univariate analysis. (A) In the overall population (NS). (B) In the MDS-IB ($p = 0.014$). There was no significant difference between these two groups in multivariable analysis. cMDS, childhood myelodysplastic syndrome; cMDS-IB, childhood myelodysplastic syndrome with increased blasts; HSCT, hematopoietic stem cell transplantation.

1.08–9.61, $p = 0.036$) and PFS (HR: 3.31, 95% CI: 1.19–9.02, $p = 0.022$) in multivariable analysis (Supporting Information S1: Table S1). This conditioning regimen was associated with a higher incidence of NRM (HR: 4.54, 95% CI: 1.43–14.34, $p = 0.010$) and grade III–IV aGvHD (HR: 5.17, 95% CI: 1.49–17.92, $p = 0.010$) in multivariable analysis.

HLA-compatibility of the donor also influenced posttransplant results (Supporting Information S1: Figure S1). A transplant from an MUD was associated with a lower probability of OS in univariate analysis (HR: 3.35, 95% CI: 1.13–9.97, $p = 0.030$) compared to MSD.

GvHD prophylaxis had no impact on OS, PFS, NRM, or incidence of aGvHD. Of note, none of the five patients transplanted from

haploidentical donors who received posttransplant cyclophophamide, experienced grade III–IV GVHD or died.

Graft source did not influence OS, PFS, NRM, or the incidence of aGvHD. However, peripheral blood stem cells as graft sources significantly increased the risk of cGVHD in multivariable analysis (HR: 17.53, 95% CI: 3.30–93.20, $p = 0.001$).

MDS-IB population—Characteristics and results

Forty patients (47.6%) presented with increased blasts at diagnosis (cMDS-IB). Their median age at transplantation was 10.3 years (IQR: 7.3–14.8). The median BM blast percentage was 8% (IQR: 5.0–14.2) at diagnosis and 4% (IQR: 0.8–8.8) at transplantation. Eighty percent of these patients had a cytogenetic abnormality, including monosomy 7 in 62% and a complex karyotype in 5%. There was no significant difference between cMDS with or without blast excess in terms of age, sex, cytogenetics, donor origin, or conditioning regimens (Supporting Information S1: Table S2). A germline predisposition was less frequently found in cMDS-IB ($p = 0.024$).

In the cMDS-IB subgroup, results were similar to those of the cohort as a whole with 5-year OS and PFS of 72% (95% CI: 59%–87%) and 63% (95% CI: 49%–81%), respectively. Overall, WHO classification and thus excess blasts at diagnosis had no influence on OS nor PFS in univariate analyses (Supporting Information S1: Table S1). Five-year cumulative incidence of NRM was 23% (95% CI: 11%–38%), twice as high as the CIR, estimated at 14% (95% CI: 5%–27%). Six-month cumulative incidences of grade II–IV and grade III–IV aGvHD were 53% (95% CI: 35%–67%) and 25% (95% CI: 13%–39%), respectively. Five-year cumulative incidences of cGVHD and extensive cGVHD were 27% (95% CI: 13%–42%) and 16% (95% CI: 6.4%–31%), respectively.

Analysis of factors associated with posttransplant outcomes in the cMDS-IB population

Half of cMDS-IB patients (20/40) received pretransplant cytoreductive therapy. These patients differed from untreated patients for median medullar blastosis at diagnosis (13.5% vs. 6.8%, respectively, $p = 0.003$) and the type of conditioning regimen (BuCyMel conditioning: 0% vs. 25% respectively, $p = 0.04$), but were otherwise comparable (Supporting Information S1: Table S3). Of the 20 patients treated, 14 (70%) achieved complete cytological remission. In univariate analysis, pretransplant cytoreduction of cMDS-IB patients was associated with a significant improvement in OS (Figure 3B), PFS, and GRFS. Intriguingly, pretransplant cytoreductive therapy had no significant impact on the risk of relapse (HR: 1.89, 95% CI: 0.33–10.84, $p = 0.470$) in univariate analysis. However, pretransplant cytoreductive therapy was associated with a significant decrease in NRM (HR: 0.12, 95% CI: 0.02–0.95, $p = 0.045$) in univariate analysis. None of these results were confirmed in multivariable analysis.

As in the overall population, in univariate analysis, other factors associated with lower OS were age below 12 years ($p = 0.05$), BuCyMel conditioning ($p = 0.006$), and transplant from an MUD donor ($p = 0.010$). None of these factors was significantly associated with OS in multivariable analysis.

DISCUSSION

In this retrospective study evaluating the results of allo-HSCT in a French multicenter cohort of 84 children treated for c-MDS, OS, and PFS at 5 years were 67% and 63%, respectively. Five-year NRM (26%) was more than twice as high as the incidence of relapse (12%).

A steady improvement in survival between 2000 and 2020 was demonstrated. This seems to be mainly explained by a significant decrease in NRM over time, reflecting improvements in supportive care and allo-HSCT procedures.

OS and PFS results in this cohort are comparable to those previously reported for patients with cMDS-IB. The main issue associated with allo-HSCT in this setting appears to be NRM (26%). In the present study, toxic mortality was mainly attributed to the high incidence of aGvHD, accounting for 15 of the 21 toxic deaths reported. The cumulative incidence of aGvHD observed here is consistent with those previously reported by the EWOG-MDS group, where grade II–IV aGvHD rates were around 45%.[6,10]

Given the high incidence of aGvHD in cMDS,[6,10] its prophylaxis is an important issue. In this series, the type of GvHD prophylaxis had no impact on OS, PFS, NRM, or incidence of aGvHD. Although it is impossible to conclude on this small number of patients, none of the five patients who received PTCy experienced grade III–IV aGHVD or died. An American series reporting the results of allo-HSCT in 22 adolescents and young adults with GATA-2 mutations showed an incidence of grade III/IV aGvHD of 32% for MSD or MUD using tacrolimus and methotrexate for GvHD prophylaxis.[19,20] As in the present series, no grade III/IV aGvHD was described after allo-HSCT was performed on haploidentical donors with PTCy.[19,20] Updated results from this US study have shown a benefit of PTCy in patients transplanted with MRD or MUD.[19] Prospective data on the use of PTCy in cMDS are therefore needed.

The type of conditioning in cMDS needs to be considered. In univariate and multivariable analysis, BuCyMel conditioning was associated with a disadvantage in OS, PFS, and GRFS. This was mainly explained by a significant increase in NRM. Singularly, BuCyMel conditioning was associated with a higher frequency of grade III–IV aGvHD. High rates of NRM and aGvHD have already been reported with BuCyMel conditioning in cMDS, JMML,[12,21] and AML.[22,23] BuCyMel is, however, the conditioning regimen currently recommended by the EWOG-MDS group for cMDS-IB. This recommendation could be challenged by data from this study.

The question of whether treatment to reduce the number of blasts should be performed before allo-HSCT in cMDS is also highly debated. In the series presented here, pretransplant cytoreductive therapy was not associated with an improvement in OS, considering the whole population. However, in the subgroup of patients presenting with cMDS-IB, pretransplant cytoreductive therapy appeared to be associated with a significant improvement of OS, PFS, and GRFS in univariate analysis. Surprisingly, the benefit of pretransplant cytoreductive therapy did not appear to be associated with a reduced risk of relapse, but with a reduction in NRM in univariate analysis. Multivariable analysis failed to confirm these results. It should be noted that due to the rarity of this pathology, the size of this cohort is relatively small ($n = 40$) and the number of events was low. This may have limited the statistical power of this study to demonstrate a significant difference. These results should also be cautiously considered as only non-pretreated patients received BuCyMel conditioning, which is associated with an increased NRM.[17-20] However, after the exclusion of patients who had received BuCyMel conditioning, a trend toward a benefit from cytoreductive therapy persisted for cMDS-IB (HR: 0.01, 95% CI: 0.00–7.38, $p = 0.176$). In addition, without reaching statistical significance, the incidence of aGvHD appeared to be higher in patients who did not receive cytoreductive therapy in the cMDS-IB group. An early reduction of immunosuppressive therapies could have been performed for these high-risk patients in the absence of pretransplant cytoreductive therapy and could explain the increased incidence of aGvHD.

Although they should be taken with caution due to the limited size of the cohort, these data are among the first to support the value

of pretransplant cytoreduction in pediatric cMDS-IB. Indeed, the EWOG-MDS-98 study showed no advantage to pretransplant cytoreductive therapy for patients with less than 20% marrow blasts.[12] Previous chemotherapy was also associated with a disadvantage in OS in a Japanese study including 242 patients transplanted for cMDS, in univariate analysis. This trend was not confirmed in multivariable analysis. Nevertheless, the authors did not report any analysis of the MDS-IB subgroup.[13] A recent single-center retrospective series showed no benefit to cytoreduction in 62 patients with MDS and related disorders. However, in this study, the population was heterogeneous and different from that of the study presented here, as it contained 29% of treatment-related myeloid neoplasms including AML. The median percentage of BM blasts at diagnosis in patients who received pretransplant cytoreduction was therefore higher than in our series (38% vs. 13.5% respectively).[24] In this US study, cytoreduced patients who achieved MRD-negative status prior to HSCT demonstrated better OS compared to those with persistent disease. In adults, paradoxically, large retrospective multicenter studies have shown that the percentage of BM blasts at the time of transplantation significantly influences the outcome after allo-HSCT for MDS.[25,26] However, for adult patients, the benefit of intensive pretransplant chemotherapy remains unclear.[27,28] Pretransplant cytoreductive therapy is generally considered when marrow blasts are over 10%, particularly for nonmyeloablative allo-HSCT,[28] and for fit patients without unfavorable cytogenetics. In adult MDS, a meta-analysis of 18 studies showed that outcomes were similar for patients who received cytoreductive therapy prior to transplantation and upfront transplantation in terms of OS, PFS, NRM, and CIR. Interestingly, achieving complete remission prior to transplantation was associated with increased PFS (HR: 0.80; 95% CI: 0.63–1.00) and decreased NRM (HR: 0.53; 95% CI: 0.32–0.90) compared with upfront transplantation.[29]

Although not significant in multivariable analysis, this study suggests that cytoreductive therapy prior to transplantation may be associated with improved OS in the subgroup of cMDS-IB patients. Surprisingly, this improvement was not related to a reduction in the risk of relapse but seems to be related to lower toxic mortality. The protective role of pretransplant cytoreductive therapy in the occurrence of aGvHD needs to be confirmed prospectively and supported pathophysiologically. In addition, the value of less toxic pretransplant cytoreductive therapy as demethylating agents[30,31] or venetoclax,[32] widely used in adult MDS, should be evaluated in the pediatric setting.

AUTHOR CONTRIBUTIONS

Baptiste Le Calvez, Audrey Grain, Maxime Jullien, and Fanny Rialland designed, performed, coordinated the research, analyzed, interpreted the data, and wrote the manuscript. Maxime Jullien and Baptiste Le Calvez performed the statistical analyses. All authors critically reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

Baptiste Le Calvez research is funded by the non-profit organization Etoile de Martin/SFCE.

ORCID

Baptiste Le Calvez http://orcid.org/0000-0001-5148-3792

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

1. Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. *J Clin Oncol*. 2017;35(9):1018-1028. doi:10.1200/JCO.2016.70.8644
2. Locatelli F, Strahm B. How I treat myelodysplastic syndromes of childhood. *Blood*. 2018;131(13):1406-1414. doi:10.1182/blood-2017-09-765214
3. Neukirchen J, Schoonen WM, Aul C, Haas R, Gattermann N, Germing U. Incidence and prevalence of patients with myelodysplastic syndromes (MDS) in Düsseldorf 1996–2005. *Blood*. 2009;114(22):1774. doi:10.1182/blood.V114.22.1774.1774
4. Drazer MW, Kadri S, Sukhanova M, et al. Prognostic tumor sequencing panels frequently identify germ-line variants associated with hereditary hematopoietic malignancies. *Blood Adv*. 2018;2(2):146-150. doi:10.1182/bloodadvances.2017013037
5. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood*. 2017;130(4):424-432. doi:10.1182/blood-2017-02-735290
6. Keel SB, Scott A, Sanchez-Bonilla M, et al. Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. *Haematologica*. 2016;101(11):1343-1350. doi:10.3324/haematol.2016.149476
7. Schwartz JR, Ma J, Lamprecht T, et al. The genomic landscape of pediatric myelodysplastic syndromes. *Nat Commun*. 2017;8(1):1557. doi:10.1038/s41467-017-01590-5
8. Starý J, Locatelli F, Niemeyer CM, on behalf of the European Working Group on Myelodysplastic Syndrome (EWOG-MDS) and Pediatric Diseases Working Party of the EBMT. Stem cell transplantation for aplastic anemia and myelodysplastic syndrome. *Bone Marrow Transplant*. 2005;35(S1):S13-S16. doi:10.1038/sj.bmt.1704836
9. Strahm B, Locatelli F, Bader P, et al. Reduced-intensity conditioning in unrelated donor transplantation for refractory cytopenia in childhood. *Bone Marrow Transplant*. 2007;40(4):329-333. doi:10.1038/sj.bmt.1705730
10. Sasaki H, Manabe A, Kojima S, et al. Myelodysplastic syndrome in childhood: a retrospective study of 189 patients in Japan. *Leukemia*. 2001;15(11):1713-1720. doi:10.1038/sj.leu.2402271
11. Woods WG, Barnard DR, Alonzo TA, et al. Prospective study of 90 children requiring treatment for juvenile myelomonocytic leukemia or myelodysplastic syndrome: a report from the Children's Cancer Group. *J Clin Oncol*. 2002;20:434-440.
12. Strahm B, Nöllke P, Zecca M, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome in children: results of the EWOG-MDS 98 study. *Leukemia*. 2011;25(3):455-462. doi:10.1038/leu.2010.297
13. Yamamoto S, Kato M, Watanabe K, et al. Prognostic value of the revised International Prognostic Scoring System five-group cytogenetic abnormality classification for the outcome prediction of hematopoietic stem cell transplantation in pediatric myelodysplastic syndrome. *Bone Marrow Transplant*. 2021;56(12):3016-3023. doi:10.1038/s41409-021-01446-z
14. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP–EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51(4):610-611. doi:10.1038/bmt.2015.305
15. Martin PJ, Lee SJ, Przepiorka D, et al. National Institutes of Health Consensus development project on criteria for clinical trials in

chronic graft-versus-host disease: VI. the 2014 clinical trial design working group report. *Biol Blood Marrow Transplant*. 2015;21(8):1343-1359. doi:10.1016/j.bbmt.2015.05.004

16. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10. doi:10.1016/j.bbmt.2015.09.001
17. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706. doi:10.1002/(SICI)1097-0258(19990330)18:6<695::AID-SIM60>3.0.CO;2-O
18. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703-1719. doi:10.1038/s41375-022-01613-1
19. Nichols-Vinueza DX, Parta M, Shah NN, et al. Donor source and post-transplantation cyclophosphamide influence outcome in allogeneic stem cell transplantation for GATA2 deficiency. *Br J Haematol*. 2022;196(1):169-178. doi:10.1111/bjh.17840
20. Parta M, Shah NN, Baird K, et al. Allogeneic hematopoietic stem cell transplantation for GATA2 deficiency using a busulfan-based regimen. *Biol Blood Marrow Transplant*. 2018;24(6):1250-1259. doi:10.1016/j.bbmt.2018.01.030
21. Mårtensson T, Priftakis P, Casswall T, et al. Increased risk of gastrointestinal acute GVHD following the addition of melphalan to busulfan/cyclophosphamide conditioning. *Pediatr Tranplant*. 2013;17(3):285-293. doi:10.1111/petr.12061
22. Lucchini G, Labopin M, Beohou E, et al. Impact of conditioning regimen on outcomes for children with acute myeloid leukemia undergoing transplantation in first complete remission. An analysis on behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transpl*. 2017;23(3):467-474. doi:10.1016/j.bbmt.2016.11.022
23. Versluys AB, Boelens JJ, Pronk C, et al. Hematopoietic cell transplant in pediatric acute myeloid leukemia after similar upfront therapy; a comparison of conditioning regimens. *Bone Marrow Transplant*. 2021;56(6):1426-1432. doi:10.1038/s41409-020-01201-w
24. Wachter F, Hebert K, Pikman Y, et al. Impact of cytoreduction and remission status on hematopoietic cell transplantation outcomes in pediatric myelodysplastic syndrome and related disorders. *Pediatr Blood Cancer*. 2023;70(9):e30530. doi:10.1002/pbc.30530
25. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129(13):1753-1762. doi:10.1182/blood-2016-06-724500
26. Sierra J, Pérez WS, Rozman C, et al. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. *Blood*. 2002;100(6):1997-2004.
27. Runde V, de Witte T, Arnold R, et al. Bone marrow transplantation from HLA-identical siblings as first-line treatment in patients with myelodysplastic syndromes: early transplantation is associated with improved outcome. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 1998;21(3):255-261. doi:10.1038/sj.bmt.1701084
28. Fenaux P, Haase D, Santini V, Sanz GF, Platzbecker U, Mey U. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(2):142-156. doi:10.1016/j.annonc.2020.11.002
29. Wang H, Li Y, Zhou W, Wang R, Li Y, Yu L. Pre-transplant therapy for patients with myelodysplastic syndromes: a systematic review and meta-analysis. *Leuk Res*. 2021;110:106645. doi:10.1016/j.leukres.2021.106645
30. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies. *J Clin Oncol*. 2012;30(36):4533-4540. doi:10.1200/JCO.2012.44.3499
31. Festuccia M, Baker K, Gooley TA, Sandmaier BM, Deeg HJ, Scott BL. Hematopoietic cell transplantation in myelodysplastic syndromes after treatment with hypomethylating agents. *Biol Blood Marrow Transplant*. 2017;23(9):1509-1514. doi:10.1016/j.bbmt.2017.05.034
32. Yang TT, Song XL, Zhao YM, et al. Outcome after allogeneic hematopoietic stem cell transplantation following venetoclax-based therapy among AML and MDS patients. *Ann Hematol*. 2022;101(12):2731-2741. doi:10.1007/s00277-022-04983-9