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# Allogeneic Stem Cell Transplantation in Therapy-Related Myelodysplasia after Autologous Transplantation for Lymphoma: A Retrospective Study of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy

Daniel Jaimes-Albornoz, Lionel Mannone, Stephanie Nguyen-Quoc, Yves Chalandon, Patrice Chevallier, Mohamad Mohty, Mathieu Meunier, Marie Robin, Marie-Pierre Ledoux, Gaelle Guillerm, et al.

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1           **Allogeneic stem cell transplantation in therapy-related**  
2           **myelodysplasia after autologous transplantation for**  
3           **lymphoma: a retrospective study of the SFGM-TC**

4

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33

34 **Running title:** Allogeneic transplant in secondary myelodysplasia.

35

36 **Key words:** Allogeneic stem cell transplantation, therapy-related myelodysplasia,

37 autologous stem cell transplantation, lymphoma.

38

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50 **ABSTRACT**

51

52 Therapy-related myelodysplastic syndrome (t-MDS) after autologous stem-cell  
53 transplantation (ASCT) is a rare complication with no curative option. Allogeneic  
54 hematopoietic stem cell transplantation (allo-HSCT) may be considered for eligible  
55 patients and has been understudied in t-MDS. We report 47 consecutive patients with  
56 t-MDS after an ASCT who underwent allo-HSCT with a median age of 58 years  
57 (range: 30-71) at transplantation and a median follow-up of 22 months (range: 0.7-  
58 107). The median overall survival (OS) was 6.9 months (95% confidence interval, 0-  
59 19). OS rates were 45% (29-60%) and 30% (15-45%) at 1 and 3 years after  
60 transplantation, respectively. On univariate analysis prior therapy for t-MDS before  
61 allo-HSCT ( $p=0.02$ ) and mismatched donors ( $p=0.004$ ) were associated with poor OS.  
62 Three-year non-relapse mortality (NRM) and relapse rates were 44% (25-63%) and  
63 41% (22-61%), respectively. Mismatched donors ( $p<0.001$ ) were associated with  
64 higher NRM and a high-risk MDS ( $p=0.008$ ) with a higher relapse risk. On  
65 multivariate analysis HLA mismatch was associated with higher NRM (HR 6.21; 95%  
66 CI 1.63-23.62;  $p=0.007$ ).

67 In conclusion, our results suggest that one third of the patients who develop t-MDS  
68 after an ASCT for lymphoma are cured after an allo-HSCT. The use of mismatched  
69 donors with standard GVHD prophylaxis should be avoided in such indication for  
70 allo-HSCT. It will be worth to see if the implementation of CY post-transplantation  
71 will improve the outcome with mismatched donors.

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## 75 INTRODUCTION

76 Treatment options for lymphoid neoplasms include autologous stem-cell  
77 transplantation (ASCT). ASCT may be used for the treatment of relapsed or refractory  
78 follicular, diffuse large B-cell, Hodgkin's, or T-cell lymphoma and is associated with  
79 improved remission rates and prolonged survival.<sup>1-3</sup> Adequate patient selection and  
80 advances in supportive care have improved outcomes of intensive chemotherapy in  
81 recent years. However, such prolongation of survival is also associated with late  
82 complications, such as the development of myeloid neoplasm consecutive to the  
83 treatment received, including the conditioning chemotherapy of ASCT.<sup>4-6</sup>

84 The risk of developing therapy-related myelodysplastic syndrome (t-MDS) or acute  
85 myeloid leukemia (t-AML) secondary to the use of both alkylating agents and  
86 topoisomerase inhibitors ranges from 5 to 7% in most series, although there are  
87 studies with very variable and extreme incidences between 1% at 30 months to 11.7%  
88 at six years and may continue to increase until 12-15 years after ASCT.<sup>7,8</sup>

89 Therapy-related MDS is associated with a high incidence of cytogenetic  
90 abnormalities, with frequent deletions or monosomies of chromosomes 5 and 7.<sup>8,9</sup>  
91 These abnormalities have been described after the use of alkylating agents,  
92 confirming their role in the development of myelodysplasia.<sup>7,8</sup> Most cytogenetic  
93 alterations and acquired mutations are associated with a poor prognosis linked to a  
94 low response to chemotherapy and short duration of remission.<sup>10,11,12</sup>

95 Although allo-SCT has been widely studied in the context of t-AML studies focusing  
96 on t-MDS are rare. Furthermore, the best time to perform allogeneic allo-HSCT in  
97 this group of patients is unknown as well as predictors that might help patient  
98 selection are lacking.<sup>13,14</sup>

99 We thus launched a retrospective multicentric study to evaluate the results of all  
100 consecutive allogeneic transplantation in population MDS secondary to autologous  
101 SCT for lymphoma

102

## 103 **PATIENTS AND METHODS**

104

### 105 **Data collection**

106 The registry coordinated by the Francophone Society of Bone Marrow  
107 Transplantation and Cellular Therapy (SFGM-TC) of the European Project Manager  
108 Internet Server database (ProMISe) was used as the data source. An electronic letter  
109 of authorization for the collection and use of the data for this retrospective study was  
110 sent to each center. All patients had given written consent before transplant for data  
111 collection in ProMISe for future research, in accordance with the Declaration of  
112 Helsinki. The scientific council of the SFGM-TC approved this study on February 2,  
113 2017.

114

### 115 **Patient selection**

116 For this retrospective study, we considered all consecutive adult patients who received  
117 an allogeneic transplant for the treatment of t-MDS to ASCT for lymphoid neoplasms  
118 registered from 2006 to 2016 in the ProMISe SFGM-TC database.

119 Patients who received an ASCT and developed secondary t-AML or those who had t-  
120 MDS which progressed to t-AML before allo-HSCT were not included. Patients who  
121 received ASCT due to neoplasms other than lymphoid neoplasms were not included.

122

### 123 **Definitions**

124 Lymphoid neoplasms were categorized according to the WHO 2008 classification.  
125 The types of MDS followed the WHO 2008 criteria for MDS and were adapted to the  
126 WHO 2016 classification.<sup>15</sup> The cytogenetic classification was assessed according to  
127 the IPSS score.<sup>16</sup> Lower-risk MDS comprised MDS with low-risk and intermediate-1  
128 risk IPSS scores, and higher risk MDS those with intermediate-2 and high-risk IPSS  
129 scores. MDS-EB-1 and MDS-EB-2 were defined according to WHO and were  
130 analyzed together. The other categories of MDS with <5% blasts in bone marrow  
131 (MDS SLD, MDS MLD, MDS-RS-SLD, MDS-RS-MLD, MDS del(5q), MDS-U)  
132 were analyzed together. The response criteria in MDS in patients who received some  
133 type of treatment after or before allo-HSCT was defined according to the International  
134 Working Group response criteria<sup>17</sup>.

135 Acute GvHD was described according to the criteria of the International Bone  
136 Marrow Transplantation Registry.<sup>17</sup> For the analysis of CMV serostatus, the most  
137 hazardous combination, defined as a CMV-seronegative recipient and CMV-  
138 seropositive donor, was compared with the other possible combinations. Intensity of  
139 the allo-HSCT conditioning regimen was analyzed according to previously  
140 established working definitions.<sup>18</sup> Only two categories were considered in the  
141 analysis: myeloablative and reduced-intensity conditioning, due to the multiple  
142 schemes and doses used. HLA mismatch was defined as the presence of at least one  
143 difference in the HLA-A, -B, -Cw, DR, or DQ loci. For the analysis, no mismatch  
144 HLA comprised identical-sibling donor and matched unrelated donor 10/10 (MUD),  
145 and HLA mismatched those with mismatched unrelated donor 9/10 (MMUD) and  
146 cord blood units 4/6 and 5/6.

147 Overall Survival (OS) was defined as the period from the day of allo-HSCT until the  
148 day of death from any cause or date of the last recorded follow-up.

149 Non-relapse mortality (NRM) was defined as death from any cause other than relapse  
150 of MDS, including progression to AML, from the day of allo-HSCT.

151 Relapse was defined as a relapse of MDS or progression to AML according to the  
152 WHO criteria.

153

#### 154 **Statistical analysis**

155 The characteristics of the patients and the factors related to lymphoma, ASCT, t-  
156 MDS, and allo-HSCT are summarized with descriptive statistics. The primary  
157 endpoint of the study was OS, which was calculated using the Kaplan-Meier method.  
158 The frequency of NRM and relapse was calculated by cumulative incidences.

159 The prognostic effects of the factors with respect to OS, NRM, and relapse were  
160 analyzed with a log-rank test (Mantel-Cox) by univariate analysis. The multivariate  
161 analysis was performed using the potential predicting factors that were significant by  
162 univariate analysis with Cox proportional hazards regression models. The calculations  
163 were performed with SPSS software version 23.0.

164

#### 165 **RESULTS**

166 To date, the French ProMISe database includes 74,779 autologous transplant and  
167 38,860 allogeneic transplant observations from 98 centers in France, Belgium, and  
168 Switzerland. We searched the French ProMISe database for all registered patients  
169 from January 2006 to December 2016. A total of 47 patients who met the inclusion  
170 criteria were included.



171 **Lymphoma and ASCT**

172 The initial neoplasm for eight patients (17.0%) was a Hodgkin Lymphoma, whereas it  
173 was a Non-Hodgkin Lymphoma for 37 (78.7%) (Table 1). Fourteen patients (29.8%)  
174 received more than two lines of chemotherapy before autologous transplantation  
175 (range 0-8). Conditioning consisted in Carmustine – Etoposide – Cytarabine –  
176 Melphalan (BEAM) for 80.8% of patients and other regimens for only 19.2%. Thirty-  
177 seven patients (78.7%) achieved complete remission. There were no patients with  
178 relapsed lymphoma at the time of allo-HSCT, but it is unknown whether there were  
179 patients who relapsed or progressed from lymphoma between ASCT and allo-  
180 HSCT. There were no patients who relapsed from lymphoma after allo-HSCT.

181

182 **MDS**

183 The median time from ASCT to the diagnosis of t-MDS was 74.4 months (range 2.2-  
184 259). Eleven patients (23.5%) had MDS-EB-1, 12 (25.6%) MDS-EB-2, and 22  
185 (46.7%) other types of MDS. No diagnostic information was obtained for two patients  
186 (4.2%).

187 Cytogenetic data were obtained for 41 patients: 82.9% had at least one cytogenetic  
188 abnormality. The most frequent cytogenetic anomalies were on chromosomes 7 (11  
189 patients, 23.4%) and 5 (six patients, 12.8%) or both of those (fifteen patients, 31.9%).

190 Among the patients, 23.4% were considered to be at low risk and 59.6% at high-risk.

191 Sixty-eight percent of patients received at least one treatment line before allo-HSCT:  
192 16 (34.1%) received hypomethylating agents and 11 (23.4%) AML-like induction  
193 treatment. Ten patients (21.3%) achieved complete remission before transplantation  
194 and 36 (76.6%) were not in complete remission prior to allo-HSCT.

195

196 **HSCT**

197 The characteristics of the patients at allo-HSCT are shown in Table 2.

198 The median age at allo-HSCT was 58 years (range: 30 - 71 years) and most of the  
199 patients were male (78.7%). The median time interval from diagnosis of t-MDS to  
200 allogeneic transplantation was 7.9 months (range: 2.5 - 16.8).

201 Peripheral blood stem-cells (PBSC) were the source used for 87.4% of patients.  
202 Nineteen patients (40.5%) were transplanted from an HLA-identical sibling donor and  
203 17 (36.2%) from a matched unrelated donor. 10 patients (21.2%) had an mismatched  
204 unrelated donor including three patients (6.3%) received umbilical cord blood  
205 transplantation (one with a double cord). None of them received a haploidentical  
206 donor. Myeloablative conditioning (MAC) was used in nine patients (19.1%), four  
207 received a combination of busulfan/cyclophosphamide regimen (two BuCy and two  
208 CyBu), with conventional doses (12.8 mg/kg busulfan IV, 120 mg/kg  
209 cyclophosphamide), three a combination of fludarabine/busulfan with ATG (150  
210 mg/m<sup>2</sup> fludarabine, 12.8 mg/kg busulfan and various doses of ATG between 2.5 mg–5  
211 mg/kg), one fludarabine/busulfan without ATG (160 mg/m<sup>2</sup> fludarabine, 9.6 mg/kg  
212 busulfan), and one fludarabine and TBI (120 mg/m<sup>2</sup> fludarabine, 8 Gy TBI).

213 Thirty-eight patients (80.9%) received reduced intensity conditioning (RIC). 22  
214 patients received a combination of fludarabine-busulfan-based RIC with ATG or ALG  
215 (100–150 mg/m<sup>2</sup> fludarabine, 3.2–6.4 mg/kg busulfan, 2.5-5 mg/kg ATG or 5–20  
216 mg/kg ALG). 4 patients received fludarabine-busulfan-based RIC without ATG. Eight  
217 patients received fludarabine-TBI-based RIC (2Gy–8 Gy) and four patients received  
218 sequential FLAMSA-RIC.

219 Eighteen patients (38.3%) received prophylaxis with cyclosporine (CsA) and  
220 mycophenolate mofetil (MMF) and 11 (23.4%) cyclosporine and methotrexate  
221 (MTX). Twelve patients (25.5%) received only cyclosporine and six (12.8%)  
222 received other regimens. The most frequent serological status for cytomegalovirus  
223 (CMV) was 29.7% R<sup>+</sup>/D<sup>+</sup>. Thirteen transplants (27.1%) were performed with the  
224 combination R<sup>+</sup>/D<sup>-</sup>.

225 Performance status was assessed using the Karnofsky Performance Score (KPS): 29  
226 patients (61.8%) had a score of 90-100 before transplantation.

227

#### 228 **Response to allo-HSCT and complications.**

229 The median duration of post-transplant follow-up was 22 months (range 0.7-107) and  
230 median survival 6.9 months (95% CI 0-19).

231 Thirty-four patients (72.3%) were in complete response after allo-HSCT and nine  
232 patients (19.1%) had a relapse/progression post-transplantation. The response was not  
233 evaluated for four patients (8.6%) because of the early death of three and lost to  
234 follow-up one of them.

235 Acute GvHD occurred in 20 patients (42.5%), seven (14.8%) had grade I, and 13  
236 (27.7%) had a grade requiring treatment (Grade II-IV). Ten patients (21.3%)  
237 developed chronic GvHD, of whom four (8.6%) had extensive and six (12.7%)  
238 limited involvement At the time of the analysis in August 2017, there were 15  
239 relapses or progressions of which 13 died: 12 related to relapse and one could  
240 not determine the cause. 11 patients in complete remission died due to  
241 transplant complications, mainly infectious. 3 patients had early death due to

242 transplant complications without knowing the response obtained to the  
243 transplant. No deaths due to veno-occlusive disease or graft rejection were reported.  
244 The causes of death are listed in Table 3.

245

#### 246 **Univariate and Multivariate analysis of patients**

247 OS for all patients was 45% (95% confidence interval 29-60) at first year, 39% (95%  
248 CI 24-55) at 2 years and 30% (95% CI 15-45) at 3 years (Table 4 and Figure 1).  
249 Univariate analysis found that prior therapy of t-MDS with hypomethylating agents  
250 before allo-HSCT ( $p=0.02$ ) and the presence of an HLA mismatch ( $p=0.004$ ) were  
251 associated with poorer OS (Table 5). Multivariate analysis showed only a non-  
252 statistically significant association with poorer OS for patients receiving a treatment  
253 based on hypomethylating agents (HR, 3.55; 95% CI, 0.97 - 12.97;  $p=0.06$ ), and no  
254 other clinically significant factors (Table 6).

255 NRM was 35% (95% CI 18–51) at first year, 39% (95% CI 21–56) at 2 years, and  
256 44% (95% CI 25–63) at 3 years (Table 4 and Figure 1). Univariate analysis identified  
257 gender ( $p=0.02$ ), graft type ( $p=0.02$ ) mismatched unrelated donor type ( $p<0.001$ ) and  
258 the presence of an HLA mismatch ( $p=0.001$ ) to be significant risk factors (Figure 2).  
259 Multivariate analysis showed an association between the use of a mismatch unrelated  
260 donor (MMUD) and shorter survival after transplantation, relative to identical siblings  
261 or matched unrelated donors (MUD) (HR, 6.21; 95% CI, 1.63– 23.62;  $p=0.007$ )

262 The risk of relapse was 35% (95% CI 18–53) at first year, 41% (95% CI 22–61) at 2  
263 years and 41% (95% CI 22–61) at 3 years (Table 4 and Figure 1). The type of MDS  
264 and presence of marrow blasts ( $p=0.008$ ) were the most significant predictive factor  
265 of relapse in univariate analysis, however multivariate analysis did not identify the  
266 presence of marrow blasts as a significant factor of relapse.

267 **DISCUSSION**

268 This retrospective study of the SFGM-TC, which examined the experience of allo-  
269 HSCT in patients, with t-MDS after an ASCT for lymphoid neoplasm, over 10 years,  
270 showed donor mismatch to adversely affect OS. This is the first series published in  
271 this specific population. In other studies, such patients account for 7 - 32% of the  
272 sample.<sup>13,14,19-26</sup> Most of the survival data of these studies show results for a mix of  
273 patients, including those with t-AML and t-MDS exposed to multiple treatments  
274 (chemotherapy and/or radiotherapy, and not necessarily previous ASCT) and various  
275 primary diseases (solid organ neoplasms, lymphoid neoplasms, myeloid neoplasms,  
276 and congenital anomalies).

277 Although allo-HSCT has been used as a curative therapeutic modality for eligible  
278 patients, data published by several groups have shown poor long-term survival.<sup>13,14,19-  
279 <sup>21</sup> In our series, the median overall survival was 6.9 months with OS at first and third  
280 year of 45 and 30%, respectively. The high NRM and relapse rates at three years  
281 (44% and 41%, respectively) were similar to those previously reported by other  
282 studies, consistent with the poor prognosis of these patients.</sup>

283 Relapse or progression of t-MDS was the main cause of mortality (44.4%) in our  
284 study. Patients with MDS-EB-1 and MDS-EB-2 had a higher risk of relapse by  
285 univariate analysis. The association of these aggressive variants of myelodysplasia  
286 with higher relapse rates has been described in other studies on patients with various  
287 primary diseases. It is not known whether treating t-MDS before transplantation can  
288 decrease the risk of relapse or whether maintenance treatment should be started after  
289 transplant to prevent relapse. In our study, the only type of pre-transplant treatment  
290 associated with improved survival was AML-like therapy even if they had not

291 achieved CR before transplantation, in univariate analysis ( $p= 0.02$ ). The multivariate  
292 analysis shows a non-statistically significant association of hypomethylating agents  
293 before transplantation with a poorer OS (HR 3.55, 95% CI 0.97-12.97,  $p=0.06$ )  
294 regardless of the response they obtained with this treatment before transplantation, in  
295 contrast to patients with *de novo* MDS and poor risk cytogenetics, who normally  
296 benefit from this approach.<sup>28</sup> Our results are not valued for the sample size and the  
297 retrospective analysis. Prospective studies are necessary to determine the benefit of a  
298 type of treatment before transplantation<sup>27</sup> A retrospective analysis that included more  
299 patients with t-AML than t-MDS, reports relapse rates of 42% and 44% at 5 and 10  
300 years with OS of 38% and 24% respectively, when AML-like chemotherapy is used  
301 before transplantation.<sup>25</sup>

302 No patient in our study received post-transplant maintenance therapy. The use of  
303 maintenance therapy, with low doses of azacytidine after allo-HSCT<sup>28</sup> and  
304 azacytidine<sup>29</sup> or decitabine with infusion of donor lymphocytes<sup>30</sup>, has been published  
305 recently and may be worth considering. Targeted therapies, directed against mutated  
306 oncogenes, such as IDH-1, IDH-2, or FLT-3 genomic alterations, may improve the  
307 outcome of specific subsets of patients in the future.

308 Infections and GVHD were the main cause of non relapse mortality.

309 In our series there were 27 deaths, 12 were due to relapse, 8 due to infections and 3  
310 due to GVHD. The few deaths due to GVHD show the intensity of the  
311 immunosuppressive prophylaxis used, limiting the graft-versus-tumor effect,  
312 increasing the possibility of relapse and the appearance of infections. Multiple  
313 schemes and doses used in conditioning and immunosuppressive prophylaxis, testing  
314 the usual drugs, have not allowed to identify whether one scheme is superior to

315 another. A significant factor to improve survival was the absence of a mismatch by  
316 using either HLA identical-sibling or matched unrelated donors, as previously  
317 reported.<sup>14</sup> A prospective study of the SFGM-TC reported better OS (37% vs 15%,  
318 p=0.02) of patients with high-risk MDS who had identical HLA donors *versus* those  
319 who did not.<sup>31</sup> In our series, there was a lower frequency of NRM in patients with  
320 10/10 donors than 9/10 donors (HR, 6.21, 95% CI, 1.63-23.62, p=0.007), although  
321 was not significant in OS by multivariate analysis. NRM associated with  
322 mismatched HLA donors could be improved with new prophylactic strategies to  
323 counter GvHD, such as post-transplant cyclophosphamide (PT-Cy). Reports over the  
324 last years on a small number of patients with *de novo* MDS/AML and t-MN who  
325 underwent allo-HSCT show similar results for HLA identical-sibling, MUD, or  
326 haploidentical donors.<sup>32</sup> A recent retrospective series of EBMT in patients with MDS  
327 who underwent haploidentical transplants reported better OS for patients treated with  
328 PT-Cy than those who were not (OS at three years of 38% vs 28%), but with high  
329 NRM (41% vs 55%).<sup>33</sup> This modality may be an acceptable option, although the risk  
330 of relapse remains high and variations in the dose of PT-Cy have even been tested in  
331 high-risk patients with refractory MDS/AML.<sup>34</sup> Indeed, older patients were recently  
332 reported to have OS of 42%, and a relapse rate of 24% at two years.<sup>35</sup> Strategies to  
333 improve progression-free survival and decrease NRM using PT-Cy have been  
334 implemented. The ALTERGREF trial (NCT03250546), currently in the inclusion  
335 phase, will evaluate the effect of PT-Cy for prevention of GvHD in haploidentical and  
336 HLA-9/10 mismatched unrelated donors transplant.

337 The proportion of patients with high risk cytogenetic has been previously reported to  
338 be 17 - 49%.<sup>13,14,23,24</sup> In our study, 68% (32 patients) had adverse cytogenetic

339 alterations, especially abnormalities in chromosomes 5 and 7. However, the results  
340 were probably not significant for the few patients in the other risk categories.

341 The best time to perform the transplant is unknown. It is possible that rapid  
342 transplantation could reduce the risk of t-MDS/t-AML-related deterioration.<sup>25</sup>  
343 Although a higher frequency of NRM is possible if the transplant is performed  
344 beyond six months (50% vs 12.5%, p=0.03) caused by toxicity and infections due to  
345 multiple chemotherapy cycles<sup>23</sup>, we found no difference in OS or NRM. Although  
346 the median age of 58 years is higher than for other large related series and 60% of  
347 patients had a KPS  $\geq$  90, these factors did not play a significant role in survival, as in  
348 other series.<sup>12-14,20,23,25</sup>

349 Our data also do not support that factors related to the primary disease and its  
350 treatment can influence survival. Interestingly, no veno-occlusive disease was  
351 observed in this population having received a previous autologous transplantation.

352 A retrospective report of EBMT found better results in the period between 1998 and  
353 2006 than for transplants performed before 1998 (40% vs 29%, p=0.02).<sup>13</sup> We found  
354 no differences between the periods of 2006-2010 and 2011-2016, probably because  
355 support care has not changed as much in the last 10 years as during the transition from  
356 the 80's to 90's.

357 Treatment options are still limited for patients who are not candidates for allo-HSCT.  
358 Other therapeutic strategies have been tested using azacitidine or clofarabine  
359 associated with chemotherapy with encouraging results.<sup>36,37</sup>

360 The limitations of our study include the collection of retrospective data and the  
361 absence of a historical group for comparisons. Patient selection may have varied



362 between centers. The small number of patients and the low incidence of secondary  
363 myelodysplasia makes it difficult to perform a prospective study.

364 In summary, although the number of patients in this study was small, the results  
365 suggest that patients receiving an ASCT for a lymphoid neoplasm who develop t-  
366 MDS have short OS after allo-HSCT, with few long-time survivors. The use of  
367 MMUD donors with standard GvHD prophylaxis should be avoided in such  
368 indications for allo-HSCT. Studies that attempt to determine whether the  
369 implementation of Cy post transplantation would improve these outcomes with  
370 mismatched donors are still ongoing. It remains necessary to explore more  
371 alternatives and transplant strategies in this critical population.

372

### 373 **AUTHOR CONTRIBUTIONS**

374 EG and DJA designed the study, analyzed the data, and wrote the paper. All authors  
375 provided patient data, approved the study design, critically reviewed the manuscript  
376 and approved the final draft.

377

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382

### 383 **CONFLICT OF INTEREST**

384 The authors declare no conflict of interest.

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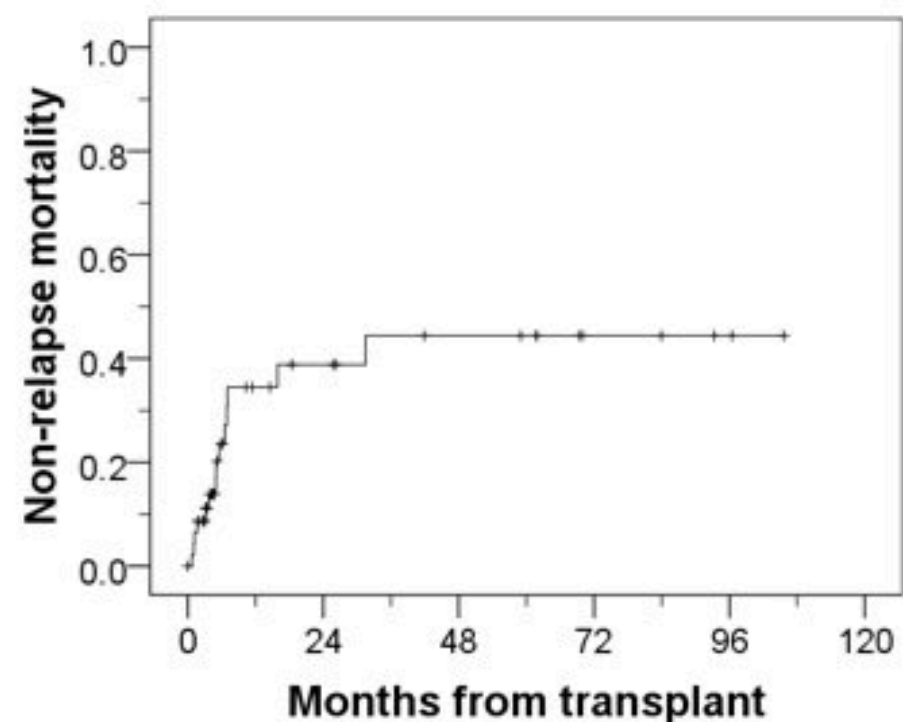
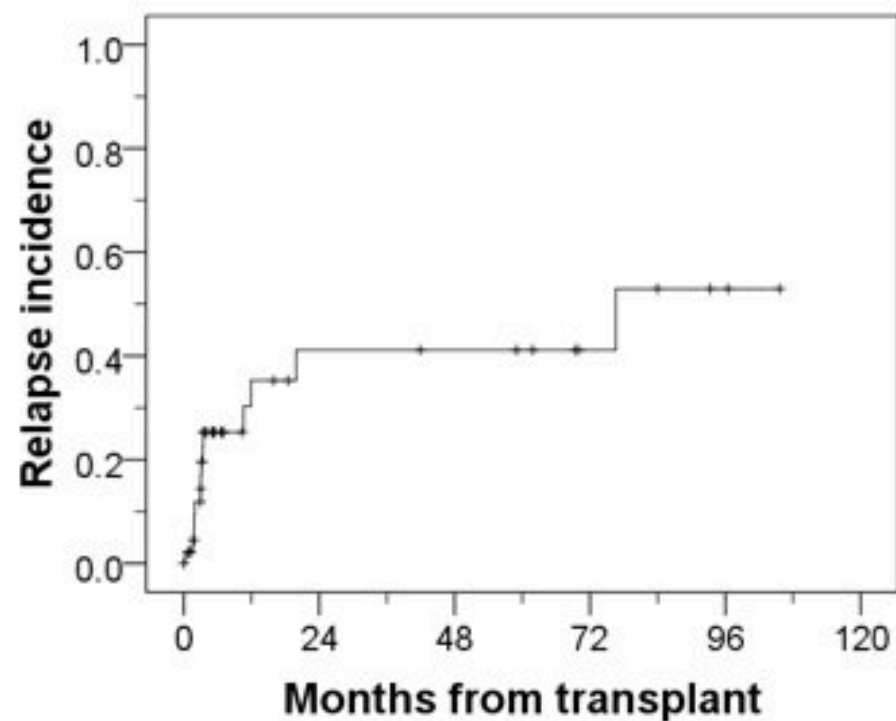
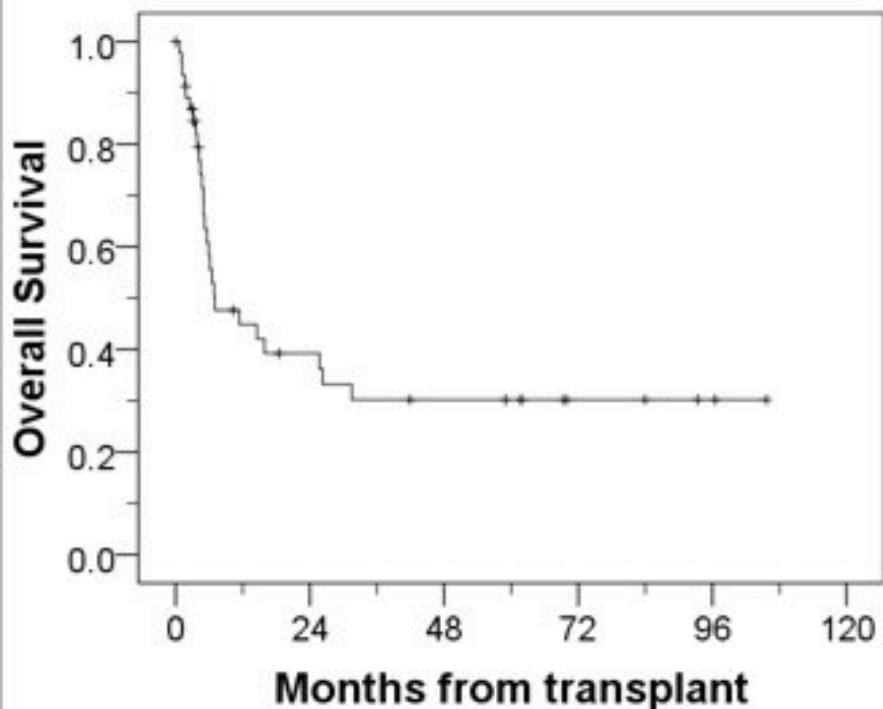
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**Figure 1. Overall survival (OS), Non-relapse mortality (NRM) and Relapse incidence of all patients who underwent allo-HSCT for a t-MDS to ASCT for lymphoid neoplasms.**

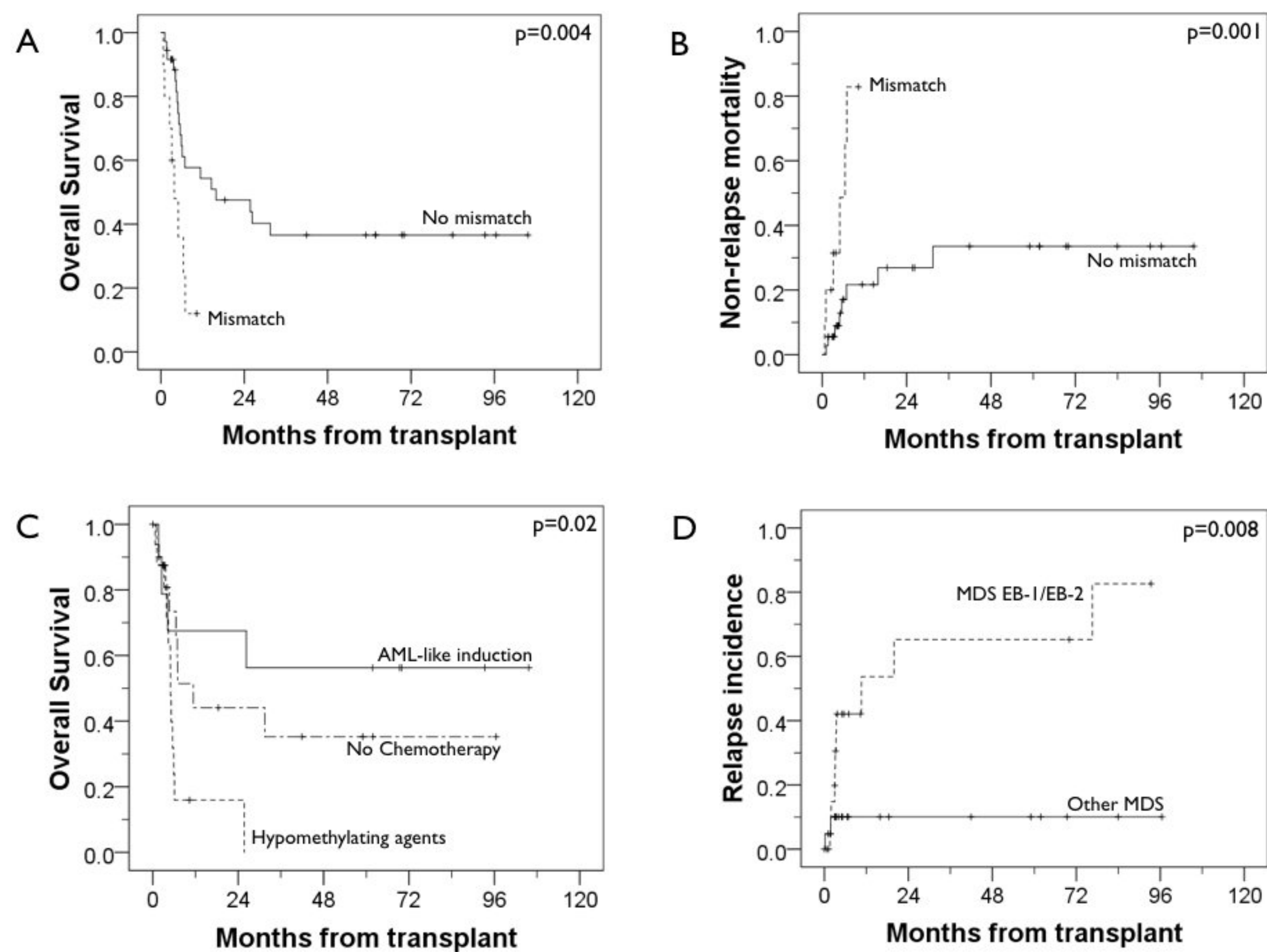


Figure 2. OS and NRM of patients with or without HLA mismatch donor (A-B). OS in regard to prior therapy of MDS before allo-HSCT (C). Relapse rate by type of MDS at diagnosis (D).

**Table 1. Patient characteristics at autologous stem cell transplantation**

Patient characteristics	Overall population, n (%)
Number of patients	47 (100)
Gender	
Male	37 (78.7)
Female	10 (21.3)
Lymphoid Hematological malignancy	
Follicular lymphoma	12 (25.6)
Diffuse Large B-cell lymphoma	12 (25.6)
Hodgkin lymphoma	8 (17.0)
Mantle cell lymphoma	5 (10.6)
Burkitt lymphoma	2 (4.3)
Nodal marginal zone lymphoma	1 (2.1)
Small lymphocytic lymphoma	1 (2.1)
Lymphoplasmacytic lymphoma	1 (2.1)
Waldenstrom macroglobulinemia	1 (2.1)
Peripheral T-cell lymphoma	1 (2.1)
Angioimmunoblastic T-cell lymphoma	1 (2.1)
Unknown	2 (4.3)
Previous lines of therapy	
1	9 (19.1)
2	24 (51.1)
≥ 3	10 (21.3)
Unknown	4 (8.5)
Conditioning ASCT	
BEAM	38 (80.8)
Chemotherapy + TBI	7 (14.9)
Unknown	2 (4.3)
Response to ASCT	
Complete remission	37 (78.7)
Not in Complete remission	4 (8.5)
Unknown	6 (12.8)

ASCT, autologous stem cell transplantation; BEAM, carmustine – etoposide – cytarabine – melphalan; TBI, total body irradiation.

**Table 2. Patient characteristics at allogeneic hematopoietic stem cell transplantation**

Patient characteristics	Overall population, n (%)
Number of patients	47 (100)
Median age at allo-HSCT, years (range)	58 (30 - 71)
Age	
≥ 58 years	23 (48.9)
< 58 years	24 (51.1)
Gender	
Male	37 (78.7)
Female	10 (21.3)
Myelodysplastic Syndrome diagnosis	
MDS-SLD	5 (10.6)
MDS-MLD	12 (25.6)
MDS-RS-SLD	1 (2.1)
MDS-RS-MLD	1 (2.1)
MDS del(5q)	1 (2.1)
MDS-EB-1	11 (23.5)
MDS-EB-2	12 (25.6)
MDS-U	2 (4.2)
Unknown	2 (4.2)
Interval from ASCT to diagnosis of t-MDS	
≥ 74 months	36 (76.5)
< 74 months	11 (23.5)
Cytogenetics	
Good/Favorable prognosis	3 (6.4)
Intermediate prognosis	6 (12.8)
Poor/Unfavorable prognosis	32 (68.0)
Unknown	6 (12.8)
IPSS diagnosis	
Low risk / Intermediate-1	11 (23.4)
Intermediate-2 / High risk	28 (59.6)
Unknown	8 (17.0)
Prior therapy of MDS before allo-HSCT	
AML-like induction treatment	11 (23.4)
Hypomethylating agents	16 (34.1)
ESA	4 (8.5)
Immunosuppressants	1 (2.1)
Nothing	11 (23.4)
Unknown	4 (8.5)
Disease status prior to allo-HSCT	
Complete remission	10 (21.3)
Not in Complete remission	36 (76.6)
Unknown	1 (2.1)
Interval from diagnosis of MDS to allo-HSCT	
< 6 months	17 (36.2)
≥ 6 months	30 (63.8)

Year of transplantation	
2006-2010	18 (38.3)
2011-2016	29 (61.7)
Conditioning regimen	
Myeloablative	9 (19.1)
Reduced intensity/non myeloablative	38 (80.9)
Conditioning regimen with TBI	
Yes	9 (19.1)
No	38 (80.9)
Graft type	
PBSC	41 (87.4)
BM	3 (6.3)
CB	3 (6.3)
Type of donor	
HLA-identical sibling (10/10)	19 (40.5)
Matched unrelated (10/10)	17 (36.2)
Mismatched unrelated (9/10, 4/6, 5/6)	10 (21.2)
Unknown	1 (2.1)
ABO Match	
Major incompatibility	15 (32.0)
Minor incompatibility	8 (17.0)
Compatible	18 (38.3)
Unknown	6 (12.7)
Sex Match	
Male/Male	21 (44.6)
Male/Female	16 (34.0)
Female/Male	4 (8.6)
Female/Female	6 (12.8)
GvHD prophylaxis	
CsA - MTX	11 (23.4)
CsA - MMF	18 (38.3)
CsA	12 (25.5)
Other	6 (12.8)
CMV serostatus	
R-/D-	12 (25.5)
R-/D+	8 (17.7)
R+/D-	13 (27.1)
R+/D+	14 (29.7)
Karnofsky score	
90-100	29 (61.8)
< 90	16 (34.0)
Unknown	2 (4.2)

HSCT, hematopoietic stem cell transplantation; MDS SLD, myelodysplastic syndrome with single lineage dysplasia; MDS MLD, myelodysplastic syndrome with multilineage dysplasia; MDS-RS-SLD, myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia; MDS-RS-MLD, myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia; MDS del(5q), myelodysplastic syndrome with isolated 5q deletion; MDS-EB-1, myelodysplastic syndrome with

excess blasts-1; MDS-EB-2, myelodysplastic syndrome with excess blasts-2; MDS-U, myelodysplastic syndrome unclassifiable; ASCT, autologous stem cell transplantation; IPSS, international prognostic scoring system; AML, acute myeloid leukemia; ESA, erythropoietin stimulating agents; TBI, total body irradiation; PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; HLA, human leukocyte antigen; GvHD, graft versus host disease; CsA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; CMV, cytomegalovirus.

**Table 3. Causes of death according to the response at allo-HSCT.**

Cause of death		CR	Not in CR	Unknown
Relapse/Progression	12 (44.4%)	4	8	
NRM causes	14 (51.9%)	11		3
Sepsis / MODS	8			
GvHD	3			
Pulmonary toxicity	1			
Hemorrhage	2			
Graft rejection	0			
VOD	0			
Unknown	1 (3.7%)	1		
<b>Total deaths</b>	<b>27 (100 %)</b>	<b>16 (59.3%)</b>	<b>8 (29.6.%)</b>	<b>3 (11.1%)</b>

HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality; MODS, multiple organ dysfunction syndrome; GvHD, graft versus host disease; VOD, veno-occlusive disease

**Table 4. Outcome of patients treated with allo-HSCT for t-MDS to ASCT for lymphoid neoplasms.**

	Non-relapse mortality	Relapse	Overall survival
At 1 year	35% (18 – 51)	35% (18 – 53)	45% (29 – 60)
At 2 years	39% (21– 56)	41% (22 – 61)	39% (24 – 55)
At 3 years	44% (25 – 63)	41% (22 – 61)	30% (15– 45)

HSCT, hematopoietic stem cell transplantation; t-MDS, therapy-related myelodysplastic syndrome; ASCT, autologous stem cell transplantation. All values are represented as % (95% confidence interval, CI).



**Table 5. Univariate analysis for probabilities of outcomes of non-relapse mortality, relapse, and overall survival at 3 years after HSCT.**

	Non-relapse Mortality (NRM)		Relapse (R)		Overall survival (OS)	
	Cumulative incidence (95% CI)	p-value	Cumulative incidence (95% CI)	p-value	Cumulative incidence (95% CI)	p-value
All probabilities estimated at 3 years						
Age at HSCT		0.23		0.21		0.69
≥ 58 years	0.43 (0.20 – 0.66)		0.37 (0.05 – 0.68)		0.33 (0.09 – 0.57)	
< 58 years	0.45 (0.18 – 0.73)		0.44 (0.20 – 0.68)		0.29 (0.09 – 0.48)	
Gender		<b>0.02</b>		0.19		<b>0.002</b>
Male	0.38 (0.17 – 0.59)		0.38 (0.16 – 0.59)		0.37 (0.18 – 0.55)	
Female	0.74 (0.34 – 1.14)		0.50 (0.15 – 0.85)		0.10 (0 – 0.29)	
Hematological malignancy		0.24		0.65		0.98
NHL	0.50 (0.29 – 0.71)		0.53 (0.22 – 0.85)		0.30 (0.13 – 0.47)	
HL	0.25 (0 – 0.68)		0.63 (0.08 – 1.17)		0.21 (0 – 0.56)	
Previous lines of therapy		0.75		0.40		0.34
1-2	0.52 (0.29 – 0.75)		0.41 (0.18 – 0.65)		0.27 (0.10 – 0.44)	
>2	0.37 (0.03 – 0.70)		0.11 (0 – 0.31)		0.48 (0.11 – 0.84)	
Conditioning ASCT		0.45		0.44		0.85
BEAM	0.44 (0.23 – 0.66)		0.39 (0.17 – 0.60)		0.31 (0.14 – 0.48)	
Others	0.57 (0.13 – 1.01)		0.20 (0 – 0.55)		0.34 (0 – 0.73)	
Conditioning ASCT		0.34		0.76		0.91
TBI	0.65 (0.26 – 1.03)		0.44 (0 – 0.93)		0.29 (0 – 0.63)	
Non-TBI	0.39 (0.19 – 0.59)		0.33 (0.13 – 0.52)		0.33 (0.15 – 0.51)	
Interval from ASCT to diagnosis of MDS		0.52		0.80		0.27
≥ 74 months	0.41 (0.16 – 0.65)		0.55 (0.20 – 0.89)		0.20 (0 – 0.39)	
< 74 months	0.43 (0.17 – 0.68)		0.36 (0.12 – 0.59)		0.39 (0.17 – 0.60)	
MDS Diagnosis		0.49		<b>0.008</b>		0.08

MDS EB-1/EB-2	0.55 (0.24 – 0.87)		0.65 (0.37 – 0.93)		0.17 (0 – 0.34)	
Other MDS	0.40 (0.14 – 0.65)		0.10 (0 – 0.23)		0.45 (0.20 – 0.70)	
IPSS diagnosis		0.25		0.94		0.64
Lower	0.21 (0 – 0.47)		0.45 (0.06 – 0.85)		0.34 (0.03 – 0.65)	
Higher	0.62 (0.37 – 0.87)		0.41 (0.11 – 0.70)		0.25 (0.06 – 0.44)	
Cytogenetics		0.40		0.27		0.40
Good prognosis	0 (0 – 0)		0 (0 – 0)		0.67	
Intermediate prognosis	0.5 (0.01 – 0.1)		0.6 (0.02 – 1.18)		0.20	
Poor prognosis	0.57 (0.31 – 0.83)		0.48 (0.21 – 0.75)		0.21	
Prior therapy for MDS before HSCT		0.12		0.21		<b>0.02</b>
AML-like therapy	0.1 (0 – 0.29)		0.38 (0.04 – 0.71)		0.56 (0.24 – 0.89)	
Hypomethylating agents	0.52 (0.21 – 0.83)		0 (0 – 0)		0 (0 – 0)	
No chemotherapy	0.51 (0.20 – 0.82)		0.42 (0.08 – 0.76)		0.35 (0.09 – 0.61)	
Year of transplantation		0.72		0.95		0.61
2006-2010	0.39 (0.14 – 0.63)		0.43 (0.15 – 0.70)		0.33 (0.12 – 0.55)	
2011-2016	0.52 (0.22 – 0.81)		0.41 (0.12 – 0.71)		0.28 (0.07 – 0.49)	
Duration of MDS from diagnosis to HSCT		0.37		0.31		0.13
< 6 m	0.36 (0.06 – 0.65)		0.22 (0 – 0.43)		0.47 (0.20 – 0.74)	
> 6 m	0.50 (0.25 – 0.75)		0.55 (0.28 – 0.81)		0.22 (0.05 – 0.39)	
Disease status prior to HSCT		0.67		0.64		0.70
Complete remission	0.25 (0 – 0.55)		0.61 (0.20 – 1.01)		0.25 (0 – 0.55)	
Partial remission	0.53 (0.10 – 0.96)		0.30 (0.01 – 0.59)		0.25 (0 – 0.53)	
Active/Progression	0.48 (0.23 – 0.74)		0.33 (0.07 – 0.58)		0.38 (0.15 – 0.60)	
MDS prior to HSCT		0.10		0.37		0.07
MDS EB-1/EB-2	0.64 (0.30 – 0.98)		0.44 (0.19 – 0.68)		0.14 (0 – 0.32)	
Other MDS	0.22 (0 – 0.45)		0.30 (0.03 – 0.56)		0.44 (0.17 – 0.71)	

IPSS prior to HSCT		0.50		0.47		0.70
Lower	0.31 (0.01 – 0.60)		0.40 (0.10 – 0.70)		0.27 (0.01 – 0.54)	
Higher	0.58 (0.25 – 0.91)		0.37 (0 – 0.75)		0.34 (0.12 – 0.58)	
Conditioning regimen		0.49		0.45		0.54
Myeloablative (MAC)	0.61 (0.21 – 1.01)		0.58 (0.18 – 0.98)		0.22 (0 – 0.49)	
Non-myeloablative/RIC	0.37 (0.18 – 0.56)		0.36 (0.15 – 0.57)		0.33 (0.15 – 0.50)	
Graft type		<b>0.02</b>		0.32		0.18
PBSC	0.31 (0.13 – 0.49)		0.37 (0.19 – 0.56)		0.36 (0.19 – 0.53)	
BM	0 (0 – 0)		0 (0 – 0)		0 (0 – 0)	
CB	0 (0 – 0)		0 (0 – 0)		0 (0 – 0)	
GvHD prophylaxis		0.95		0.24		0.55
CsA - MTX	0.49 (0.15 – 0.84)		0.35 (0.01 – 0.70)		0.40 (0.10 – 0.71)	
CsA – MMF	0.47 (0.19 – 0.75)		0.49 (0.15 – 0.82)		0.18 (0 – 0.39)	
CsA	0.17 (0 – 0.38)		0.58 (0.17 – 0.98)		0.25 (0 – 0.54)	
Other	0.33 (0 – 0.71)		0 (0 – 0)		0.67 (0.29 – 1.04)	
Type of donor		<b>&lt;0.001</b>		0.90		0.58
HLA-identical sibling	0.30 (0.04 – 0.56)		0.46 (0.19 – 0.71)		0.35 (0.12 – 0.58)	
Matched unrelated	0.36 (0.05 – 0.66)		0.33 (0.04 – 0.62)		0.40 (0.13 – 0.66)	
Mismatched unrelated	0.83 (0.53 – 1.13)		0.25 (0 – 0.55)		0.12 (0 – 0.34)	
Mismatch HLA		<b>0.001</b>		0.86		<b>0.004</b>
No (10/10)	0.34 (0.13 – 0.54)		0.41 (0.21 – 0.61)		0.37 (0.19 – 0.54)	
Yes (No 10/10)	0.83 (0.53 – 1.13)		0.25 (0 – 0.55)		0.12 (0 – 0.34)	
ABO Match		0.58		0.72		0.59
Compatible	0.49 (0.19 – 0.78)		0.46 (0.11 – 0.81)		0.19 (0 – 0.41)	
Major incompatibility	0.59 (0.21 – 0.96)		0.66 (0.30 – 1.02)		0.16 (0 – 0.36)	
Minor incompatibility	0.33 (0 – 0.87)		0.29 (0 – 0.62)		0.40 (0 – 0.83)	
Sex Match		0.50		0.66		0.40
Yes	0.37 (0.13 – 0.61)		0.35 (0.11 – 0.58)		0.36 (0.14 – 0.58)	
No	0.15 (0 – 0.44)		0.50 (0.19 – 0.81)		0.25 (0.05 – 0.45)	

CMV serostatus		0.31		0.16		0.07
R+/D-	0.60 (0.19 – 1.01)		0.64 (0.14 – 1.16)		0.12 (0 – 0.34)	
Others	0.41 (0.20 – 0.62)		0.37 (0.16 – 0.57)		0.36 (0.18 – 0.53)	
Karnofsky score		0.50		0.65		0.92
90-100	0.47 (0.24 – 0.69)		0.44 (0.20 – 0.68)		0.30 (0.12 – 0.48)	
< 90	0.27 (0 – 0.57)		0.35 (0.05 – 0.64)		0.34 (0.05 – 0.63)	
Acute GvHD		0.29		0.61		0.81
Yes	0.63 (0.34 – 0.93)		0.43 (0.08 – 0.79)		0.24 (0.02 – 0.47)	
No	0.29 (0.08 – 0.49)		0.42 (0.17 – 0.66)		0.35 (0.15 – 0.54)	

NRM, non-relapse mortality; R, relapse; OS, overall survival; HSCT, hematopoietic stem cell transplantation; NHL, non-hodgkin lymphoma; HL, hodgkin lymphoma; ASCT, autologous stem cell transplantation; BEAM, carmustine – etoposide – cytarabine – melphalan; TBI, total body irradiation; MDS, myelodysplastic syndrome; MDS-EB-1, myelodysplastic syndrome with excess blasts-1; MDS-EB-2, myelodysplastic syndrome with excess blasts-2; IPSS, international prognostic scoring system; AML, acute myeloid leukemia; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; GvHD, graft versus host disease; CsA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; HLA, human leukocyte antigen; CMV, cytomegalovirus; R: receptor; D, donor; KPS, karnofsky performance status.

**Table 6. Multivariate analysis of outcomes of non-relapse mortality, relapse, and overall survival after HSCT.**

	Overall survival (OS)		Non-relapse mortality (NRM)		Relapse (R)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Prior therapy for MDS before HSCT						
AML-like induction	1.0	0.13				
Hypomethylating agents	3.55 (0.97 - 12.97)	0.06				
No chemotherapy	1.79 (0.52 - 6.15)	0.35				
HLA Mismatch		0.13		<b>0.007</b>		
No (10/10)	1.0		1.0			
Yes (9/10, 4/6, 5/6)	2.04 (0.80 - 5.22)		6.21 (1.63 – 23.62)			
MDS Diagnosis						0.21
Other MDS					1.0	
MDS EB-1/EB-2					2.63 (0.57 – 12.03)	

NRM, non-relapse mortality; R, relapse; OS, overall survival; MDS, myelodysplastic syndrome; HSCT, hematopoietic stem cell transplantation; AML, acute myeloid leukemia; HLA, human leukocyte antigen; MDS-EB-1, myelodysplastic syndrome with excess blasts-1; MDS-EB-2, myelodysplastic syndrome with excess blasts-2.