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Comparison of mycophenolate mofetil and calcineurin inhibitor versus calcineurin inhibitor-based graft-versus-host-disease prophylaxis for matched unrelated donor transplant in acute myeloid leukemia. A study from the ALWP of the EBMT

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1 **Comparison of mycophenolate mofetil and calcineurin inhibitor versus calcineurin**
2 **inhibitor-based graft-versus-host-disease prophylaxis for matched unrelated donor**
3 **transplant in acute myeloid leukemia. A study from the ALWP of the EBMT.**

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43
44

45 **Abstract**

46 The association of Cyclosporine A (CsA) and mycophenolate mofetil (MMF) has
47 increased in the setting of reduced intensity conditioning (RIC). Nevertheless, the use of
48 CsA or CsA+MMF has not been reported in a large and uniform cohort.

49 We analyzed 497 patients with acute myeloid leukemia in complete remission (CR) who
50 underwent matched unrelated donor (MUD) hematopoietic stem cell transplantation
51 (HSCT). All patients received a fludarabine busulfan RIC regimen and anti-thymocyte
52 globulin (ATG) with either CsA alone or in combination with MMF.

53 The cumulative incidence (CI) of grade II-IV acute GvHD was 27% (95% CI 21-33%) for
54 CsA and 33% (95% CI 27-38%) for CsA+MMF ($p=0.25$). The 2-year CI of chronic GvHD was
55 38% (95% CI 31-45%) and 33% (95% CI 28-39%) for the CsA and the CsA+MMF group,
56 respectively ($p=0.26$).

57 On multivariate analysis, no statistically significant differences with respect to relapse
58 incidence (RI), non-relapse mortality (NRM), leukemia free survival (LFS), overall survival
59 (OS), acute and chronic GvHD were found between the two groups, also when
60 conducting a subgroup analysis in peripheral blood stem cells (PBSC) recipients. Our
61 results support the importance of randomized trial to identify patients who could
62 benefit from the addition of MMF in MUD HSCT.

63

64 **Introduction**

65 Allogeneic hematopoietic stem cell transplantation (HSCT) is an important and
66 potentially curative treatment option for patients with acute myeloid leukemia (AML).
67 However, long-term outcomes may be associated with an extent of non-relapse
68 mortality (NRM). Acute graft-versus-host disease (aGvHD) is one of the most common
69 causes of increased morbidity and mortality after transplant. In the setting of matched
70 unrelated donor (MUD), GvHD prophylaxis strategies include the use of
71 immunosuppressive drugs such as the calcineurin inhibitor cyclosporine A (CsA), but
72 they are poorly standardized (1) (2).

73 CsA combined with another immunosuppressive agent i.e. methotrexate (MTX) or
74 mycophenolate mofetil (MMF) has been shown to further decrease the incidence of
75 severe aGVHD and to improve survival (3) (4).

76 MMF inhibits T cell activation and proliferation, and has been used in combination with
77 CsA for GvHD prophylaxis, especially in the setting of reduced intensity regimens (5) (6)
78 (7). Compared to MTX, MMF is less toxic when used in combination with CsA (5) (8).

79 However, all of the published studies have included heterogeneous groups of patients
80 who underwent HSCT for both lymphoid and myeloid malignancies and with diverse
81 chemotherapy conditioning intensity regimens (9) (10) (11). None of the studies has
82 compared MMF and CsA with CsA alone-based GvHD prophylaxis exclusively in a large
83 cohort of patients with homogeneous disease.

84 In this study, we report the outcomes of two groups of patients who underwent MUD
85 HSCT with fludarabine and busulfan for AML in complete remission (CR) and received
86 CsA alone or CsA and MMF as GvHD prophylaxis.

87

88

89 **Materials and Methods**

90 This is a registry cohort study. We analyzed 497 adult patients, with a diagnosis of AML
91 who underwent a 10/10 MUD HSCT and received CsA alone (n=183) or CsA+MMF
92 (n=314) as GvHD prophylaxis. All patients underwent a reduced intensity conditioning
93 (RIC) regimen with fludarabine 30mg/m² from day -6 to day -2, busulfan 130mg/m²
94 from day -5 to day -4 and received anti-thymocyte globulin (ATG). Patient's human
95 leucocyte antigen (HLA)-matched to the donor at the allele-level for HLA-A, HLA-B, HLA-
96 C, HLA-DQB1 and HLA-DRB1 were included. Transplants were performed in European
97 Society for Blood and Marrow Transplantation (EBMT) centers from 2007 to 2017. All
98 patients provided written informed consent for the use of their data for clinical research,
99 in accordance with the modified guidelines of the Declaration of Helsinki and the local
100 ethics committee. The Review Board of the Acute Leukemia Working Party (ALWP) of
101 the EBMT approved this study.

102 Patients with available cytogenetic data were classified according to the Medical
103 Research Council (12).

104 The primary endpoint was the cumulative incidence (CI) of aGvHD and chronic GvHD
105 (cGvHD), defined according to standard criteria(13) (14).

106 Secondary endpoints were neutrophil engraftment, non-relapse mortality (NRM),
107 relapse incidence (RI), leukemia free survival (LFS), overall survival (OS) and graft-versus-
108 host-disease free, relapse free survival (GRFS).

109 Neutrophil engraftment was defined as the first day of an absolute neutrophil count of
110 $0.5 \times 10^9/L$ lasting for 3 or more consecutive days. OS was defined as time from HSCT to
111 death from any cause or last follow-up, whichever came first; patients alive at last follow

112 up were censored. LFS was defined as time from HSCT to relapse, death from any cause
113 or last follow-up, whichever comes first; patients alive without disease at last follow-up
114 were censored. NRM was defined as time to death from any cause not related to relapse
115 and RI was defined as time from HSCT to relapse. GRFS was defined as the time from
116 transplant to grade III-IV acute GVHD, extensive cGVHD, relapse, or death; whichever
117 came first (15).

118 CI curves were used in a competing risk setting to calculate probabilities of aGvHD and
119 cGvHD, neutrophil recovery, NRM and RI. To study acute and chronic GVHD, we
120 considered relapse and death to be competing events. Probabilities of OS, LFS and GRFS
121 were calculated using the Kaplan-Meier method. Univariate analyses were done using
122 the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS,
123 and LFS. A Cox proportional hazards model was used for multivariate regression. All
124 variables differing significantly between the two groups or factors associated with one
125 outcome in univariate analysis were included in the Cox model. In order to test for a
126 centre effect, we introduced a random effect or frailty for each centre into the
127 model(16) (17). All tests were 2-sided. The type I error rate was fixed at 0.05 for the
128 determination of factors associated with time-to-event outcomes. A subgroup analysis
129 planned from the beginning of the study was also performed on a homogeneous
130 population of patients transplanted in CR1 using PBSC. Ninety-five percent confidence
131 intervals (95% CI) were calculated. Analyses were performed with SPSS 24 (IBM SPSS
132 Statistics for Windows, Version 19.0. IBM Corp, Armonk, NY) and R 3.6.2 (R Foundation
133 for Statistical Computing, Vienna, Austria) software packages.

134

135 **Results**

136 Patient, disease, and transplant characteristics according to GvHD prophylaxis are
137 summarized in Table 1. A total of 497 patients with diagnosis of AML were included, of
138 which 183 received CsA and 314 CsA+MMF. The median follow-up was 33 (inter quartile
139 range [IQR] 18-60) months for the CsA group and 34 (IQR 18-54) months for the
140 CsA+MMF group. There were no significant differences between the groups with respect
141 to patient, disease and HSCT characteristics. The majority of patients had intermediate
142 cytogenetic risk and a performance status $\geq 90\%$.

143

144 Engraftment

145 The CI of neutrophil engraftment at 60 days was 99.4% and 99.7% in the CsA and
146 CsA+MMF group, respectively ($p=0.14$). The median time to achieve neutrophil
147 engraftment was not different between the two groups: 18 (range: 2-45) days in the CsA
148 and 19 (range: 7-37) days in the CsA+MMF cohort, $p=0.092$). Graft failure was observed
149 in one patient in the CsA group and one patient in the CsA+MMF group experienced
150 secondary graft rejection.

151

152 Acute and chronic GVHD

153 Overall, the 100-day CI of grade II-V aGvHD was 30% (95% CI 26-35%). The CI of grade II-
154 IV aGvHD did not differ between the group of patients who received CsA alone and those
155 who received CsA+MMF (27% versus 33%, $p=0.25$) (figure 1a).

156 The CI of grade III-IV aGvHD was 10% (95% CI 8-13%) at 100 day; it was 9% (95% CI 6-
157 14%) for the CsA group and 11% (95% CI 8-14%) for the CsA+MMF group ($p=0.60$) (figure
158 1b).

159 The 2 year CI of cGvHD and extensive cGvHD were 35% (95% CI 31-40%) and 15% (95%
160 CI 12-19%), respectively. According to GvHD prophylaxis, the CI of cGvHD was 38% (95%
161 CI 31-45%) and 33% (95% CI 28-39%) in patients who received CsA alone and CsA+MMF,
162 respectively (p=0.26) (figure 2a). The CI of extensive cGvHD was also comparable
163 between the two groups, being 17% (95% CI 11-23) for patients who received CsA and
164 15% (95% CI 11-19) for those who had CsA+MMF (p=0.49) (figure 2b).

165 The results of the univariate analysis are reported in the Supplementary Table 1.

166 On multivariate analysis (table 2), there was no significant difference for risk of aGvHD
167 between patients who had CsA alone versus CsA+MMF (Hazard ratio [HR] 1.18, 95% CI
168 0.79-1.78, p=0.41) nor for cGvHD (HR 0.79, 95% CI 0.53-1.17, p=0.25).

169

170

171 RI and NRM

172 The 2-year RI and NRM were 25% (95% CI 21-29%) and 19% (95% CI 16-23%),
173 respectively. RI was not significantly different between recipient who had CsA alone
174 (26% [95% CI 20-33%]) and CsA+MMF (24% [95% CI 19-29%]) (p=0.90) (figure 3b). No
175 difference was also observed in NRM according to the GvHD prophylaxis group: 21%
176 (95% CI 16-28%) for CsA alone and 18% (95% CI 14-22%) for CsA+MMF, p=0.52 (figure
177 3a).

178 On multivariate analysis (table 2), there was no difference between the two groups with
179 respect to RI (HR 0.63, 95% CI 0.37-1.06, p=0.08) and NRM (HR 0.83, 95% CI 0.52-1.33,
180 p=0.43). A positive donor CMV serology was associated with higher NRM (HR 2.03, 95%
181 CI 1.31-3.14, p=0.001). Another factor associated with increased risk of NRM was older
182 age (HR 1.39, 95% CI 1.05-1.85, p=0.02).

183 A total of 208 patients died (81 and 127 in the CsA and CsA+MMF groups, respectively).
184 In the CsA group, 39% died of relapse, 25% of GvHD, 22% of infection, 15% for other
185 causes. In the CsA+MMF group 43% of patients died of relapse, 23% of infection, 23% of
186 GvHD, 11% for other causes.

187

188 OS, LFS and GRFS

189 The 2-year OS and LFS were 60% (95% CI 55-64%) and 56% (95% CI 52-61%), respectively.
190 OS was similar between patients who had CsA alone (55% [95% CI 47-63%]) and
191 CsA+MMF (62% [95% CI 57-68%]), $p=0.67$. No differences were detected for LFS (CsA
192 group: 52% [95% CI 45-60%]; CsA+MMF: 59% [95% CI 53-64%], $p=0.56$) and GRFS (40%
193 [95% CI 32-47%] for CsA alone and 48% [95% CI 42-54%] for CsA+MMF, $p=0.37$) (figure
194 3c, 3d and figure 4).

195 On multivariate analysis (table 2), there were no differences in survival rates according
196 to GvHD prophylaxis. Patients with a donor positive CMV serology had a significantly
197 lower OS (HR 1.66, 95% CI 1.22-2.26, $p=0.001$), LFS (HR 1.69, 95% CI 1.26-2.27, $p<0.001$)
198 and GRFS (HR 1.75, 95% CI 1.34-2.28, $p<0.001$) compared with patients with a donor
199 negative CMV serology.

200

201 Subgroup analysis for patients in CR1 who received PBSC

202 We observed no differences with respect to aGvHD, cGvHD, NRM, RI, OS, LFS and GRFS
203 when analyzing patients in CR1 who received PBSC (CsA alone, $n=138$; CsA+MMF,
204 $n=257$). In univariate analysis, patients who received CsA+MMF tended to have a lower
205 cGvHD at 2 years ($p=0.053$), but this was not statistically significant in multivariate
206 analysis (HR 0.67, 95% CI 0.42-1.05, $p=0.08$).

207

208 **Discussion**

209 We observed comparable outcomes in patients with AML undergoing a RIC ATG based
210 10/10 MUD HSCT with fludarabine and busulfan as the conditioning regimen when
211 comparing two groups of GvHD prophylaxis (CsA alone versus CsA+MMF). The addition
212 of MMF to CsA was not associated with a significant reduction of acute and chronic
213 GvHD.

214 Since the introduction of the combination of MMF and CsA in the late 1990s, few studies
215 have reported transplant outcomes of MUD HSCT, thus data are scarce. Moreover,
216 published studies refer to a small number of patients.

217 In 2004, the outcomes of 34 patients who underwent RIC with a fludarabine and
218 busulfan ATG-based preparative regimen and a HLA-identical sibling as graft source
219 were compared for these two types of GvHD prophylaxis(18). Among them, 27 had
220 hematological malignancies of which 16 received CsA alone and 11 received CsA and
221 MMF. No differences in outcomes and specifically in aGvHD incidence were detected in
222 this small group of patients.

223 Similarly, a brief report retrospectively described 35 patients with both myeloid and
224 lymphoid malignancies who underwent a MUD HSCT with the same conditioning
225 regimen (19). Of these, 31 were 10/10 matched with the recipient (CsA alone, n=16; CsA
226 and MMF, n=15). Although a limited number of patients were described, the study
227 reported a better OS and a lower CI of grade III-IV aGvHD in the CsA+MMF group.

228 Another brief report showed the beneficial effect of ATG, CsA and MMF in the RIC setting
229 for cGvHD on 20 patients, of whom 12 were 10/10 matched (20). A recent phase 3 trial
230 investigating the addition of sirolimus to CsA+MMF for prophylaxis, reported higher CI

231 of grade II-IV aGvHD (up to 52%) in CsA+MMF arm and supported the benefit of adding
232 silorimus in GvHD prophylaxis. However, in contrast with our study population, in this
233 trial patients did not receive ATG (21).

234 In our study, the benefit of adding MMF regardless of the use of ATG could not be
235 analyzed. Notably, all patients received ATG, a T-cell depleting agent. It might be
236 possible that the association of ATG with the use of CsA reflects an adequate GvHD
237 prophylaxis in our cohort and indirectly prevented us in estimating the supposed benefit
238 of MMF addition, which selectively targets the activated lymphocytes(22). The
239 protective effect of ATG in reducing cGVHD and improving GRFS has recently been
240 demonstrated in a large phase clinical III trial(23), and ATG remains a recommended
241 treatment for GvHD prevention in patients undergoing MUD or HLA-sibling HSCT.

242 Recently, the type of post-transplant immunosuppression was described in patients with
243 AML in CR1 given PBSC from matched related donors with a RIC fludarabine based
244 regimen. The CsA group (n=86) was compared to a group receiving CsA+MMF/MTX
245 (n=66, CsA+MMF= 45) and to another group who did not receive ATG. The authors found
246 that the addition of MMF or MTX to CsA did not reduce the risk of aGvHD, but
247 significantly increased the risk of relapse, possibly due to the relatively reduced risk of
248 cGvHD, leading to worse LFS an OS (24).

249 In our cohort, which is similar for disease type but in MUD setting, a subgroup analysis
250 performed in patients in CR1 who received PBSC identified a tendency toward higher
251 cGvHD at 2 years for patients who received CsA alone. However, this finding was not
252 confirmed on multivariate analysis.

253 The intensity of GvHD prophylaxis did not modify the risk of relapse. We observed in
254 both groups a satisfactory OS and GRFS, which reflects the quality of life without long-
255 term complications related to the GvHD.

256 We observed a higher NRM in recipients for whom the donor had a positive CMV
257 serology that resulted in a lower LFS, GRFS and OS. This finding is in line with previous
258 reports described from the EBMT on outcomes in de novo acute leukemia (25) and from
259 the Center for International Blood and Marrow Transplant Research (CIBMTR) who
260 demonstrated that early CMV reactivation has a negative impact on transplant
261 outcomes regardless of hematological disease type (26). Finally, in our cohort older age
262 was associated with an increased risk of NRM ($p=0.02$) on multivariate analysis. This
263 finding did not result in a lower OS, indicating that older age should not be considered a
264 condition for withholding RIC HSCT in patients with AML in CR.

265 One of the limitations of our registry-based study is that some disease characteristics
266 could be confounding factors. In order to overcome this limitation, we performed a
267 subgroup analysis in a homogenous group of patients with AML in CR1 who had PBSC.

268 Although we acknowledge that due to the retrospective nature of the study recent
269 specific molecular methods such as next generation sequencing or molecular status
270 were not available, the results remained consistent with those of the entire study
271 population.

272 Although measuring the active metabolite of MMF is not a standard practice, several
273 pharmacokinetic studies on GvHD have demonstrated higher mycophenolic acid
274 concentration in responders compared with non-responders(27). The optimal duration
275 of MMF has not been established; however, some authors have reported lower
276 incidences of GvHD after a prolonged treatment (28). Due to the retrospective nature

277 of the study, we are not able to report the dosing schedule and the duration of the two
278 metabolites MMF and CsA.

279 A study conducted on 23 recipients undergoing MUD HSCT reported that interindividual
280 variations in CsA levels after 2 hours intake were not associated with a higher risk of
281 GvHD when cyclosporine trough (C0) guided the dosing (29). A more comprehensive
282 study on 85 patients receiving a MUD HSCT with either reduced or myeloablative
283 conditioning demonstrated that the lowest CsA concentration in the first and second
284 weeks after HSCT was associated with a significantly higher risk of grade III-IV aGvHD
285 (30). We were not able to further investigate these points in our study, but we did not
286 observe significant differences in transplant outcomes between the two groups
287 regarding aGvHD.

288 We acknowledge that the retrospective nature of our study could introduce another
289 bias. Preference for a particular GvHD prophylaxis is largely based on uncontrolled,
290 observational studies, and is often guided by physician or transplant center preference.
291 Conflicting results regarding various clinical outcomes have been observed when
292 comparing MMF against MTX regimens for aGvHD prophylaxis, and less is known
293 regarding CsA compared with MMF+CsA. With an increasing number of RIC HSCTs being
294 performed, it could be of importance to prospectively evaluate the comparative efficacy
295 of the two prophylactic agents in the prevention of GvHD.

296 Randomized trials analyzing the use of MMF versus placebo in the setting of RIC ATG
297 MUD HSCT should be considered to better assess which patients could eventually
298 benefit from the addition of MMF for GvHD prophylaxis.

299

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303 **Author contributions**

304 AP and MM designed the study, AP, MM and AN wrote the manuscript, ML performed
305 the statistical analysis, DB, GS, CEB, BL, PC, IWB, GG, JM, PC, AH, PT, ED, EF and AN
306 provided cases for the study. All authors edited and approved the final version of the
307 manuscript.

308 **Conflict of interest**

309 The authors have no conflict of interest to disclose

310

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428

429 **Figure 1.** Cumulative incidence of acute grade II-IV GvHD and grade III-IV GvHD according
430 to CsA alone (black continuous line) or CsA+MMF GvHD (dashed line) prophylaxis.

431 **Figure 2.** Cumulative incidence of chronic GvHD and extensive chronic GvHD according
432 to CsA alone (black continuous line) or CsA+MMF GvHD (dashed line) prophylaxis.

433 **Figure 3.** Cumulative incidence of non-relapse mortality, relapse incidence, leukemia
434 free survival and overall survival according to CsA alone (black continuous line) or
435 CsA+MMF GvHD (dashed line) prophylaxis.

436 **Figure 4.** Graft-versus-host-disease free, relapse free survival (GRFS) according to CsA
437 alone (black continuous line) or CsA+MMF GvHD (dashed line) prophylaxis.

438 **Table 1.** Disease, patient and transplant characteristics.

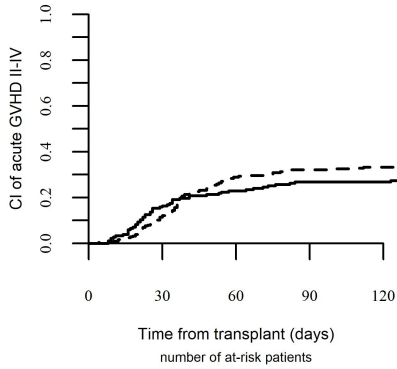
439 **Table 2.** Multivariate analysis.

Table 1. Disease, patient and transplant characteristics

| | | CsA alone (n=183) | CsA+MMF (n=314) | <i>p-value</i> |
|------------------------------|--|---|--|-----------------------|
| age at HSCT, median (range) | years | 59 (20-75) | 60 (22-75) | 0.84 |
| year of HSCT, median (range) | years | 2015 (2007-2017) | 2014 (2007-2017) | 0.08 |
| disease state at HSCT | CR1 CR2 | 149 (81%) 34 (19%) | 268 (85%) 46 (15%) | 0.25 |
| cytogenetics (MRC) | good intermediate poor missing | 10 (6%) 121 (66%) 35 (19%) 17 (9%) | 17 (5%) 209 (67%) 47 (15%) 41 (13%) | 0.45 |
| Karnofsky performance status | <90 >=90 missing | 52 (32%) 113 (68%) 18 | 78 (27%) 212 (73%) 24 | 0.29 |
| Graft source | BM PBSC | 12 (7%) 171 (93%) | 12 (4%) 302 (96%) | 0.17 |
| Gender | male female | 108 (59%) 75 (41%) | 160 (51%) 154 (49%) | 0.08 |
| Donor gender | male female missing | 129 (70%) 54 (30%) 0 | 195 (63%) 113 (37%) 6 | 0.10 |
| Gender matching | no female to male female to male missing | 159 (87%) 24 (13%) 0 | 265 (85%) 46 (15%) 3 | 0.60 |
| Patient CMV serology | negative positive missing | 76 (42%) 107 (58%) 0 | 118 (38%) 192 (62%) 4 | 0.45 |
| Donor CMV serology | negative positive missing | 119 (65%) 63 (35%) 1 | 183 (60%) 124 (40%) 7 | 0.20 |

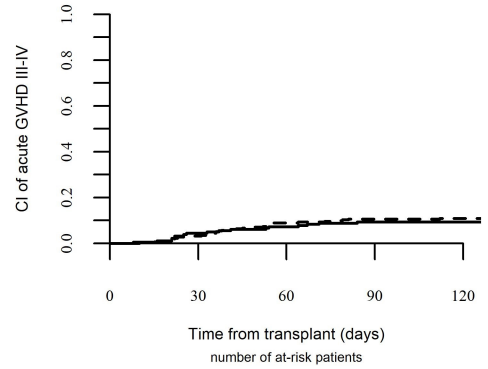
Abbreviations: HSCT, hematopoietic stem cell transplantation; CsA, cyclosporine A; MMF, mycophenolate mofetil; CR, complete remission; BM, bone marrow; PBSC, peripheral blood stem cells; CMV, cytomegalovirus; MRC, Medical Research Council

acute GVHD II-IV



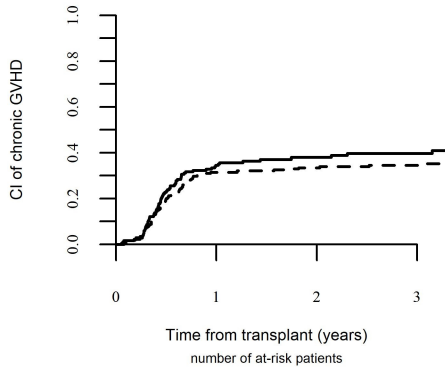
| | | | | | | |
|-------|-----------|-----|-----|-----|-----|-----|
| — | CSA alone | 183 | 152 | 134 | 122 | 183 |
| - - - | CSA+MMF | 108 | 314 | 274 | 213 | 108 |

acute GVHD III-IV



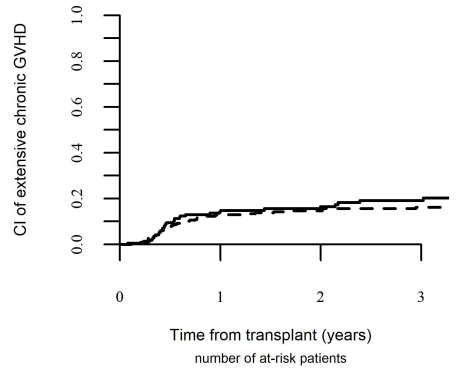
| | | | | | | |
|-------|-----------|-----|-----|-----|-----|-----|
| — | CSA alone | 181 | 171 | 160 | 151 | 181 |
| - - - | CSA+MMF | 136 | 312 | 297 | 271 | 136 |

cGVHD



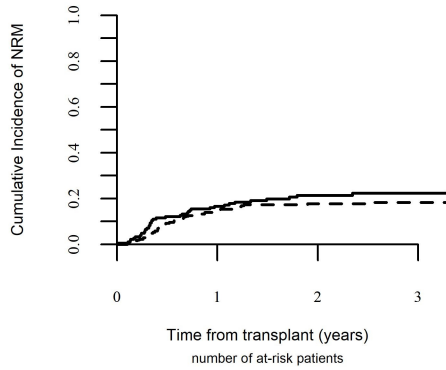
| | | | | |
|-------------|-----|-----|----|----|
| — CSA alone | 183 | 61 | 30 | 24 |
| - - CSA+MMF | 314 | 115 | 74 | 54 |

extensive cGVHD

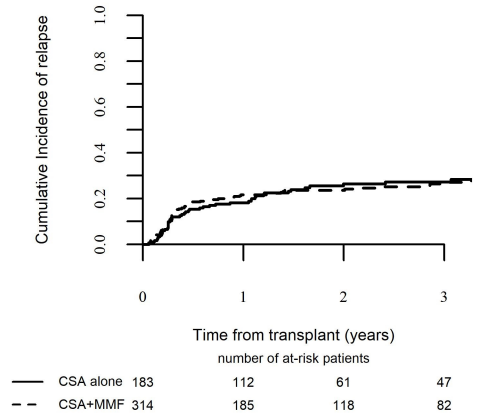


| | | | | |
|-------------|-----|-----|-----|----|
| — CSA alone | 170 | 86 | 46 | 34 |
| - - CSA+MMF | 307 | 160 | 104 | 71 |

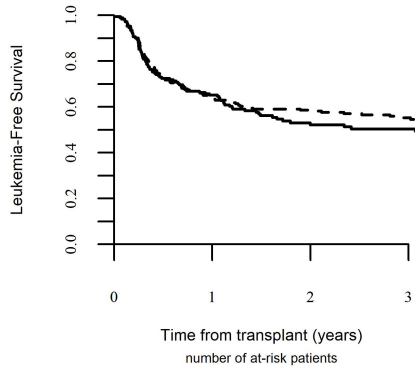
NRM



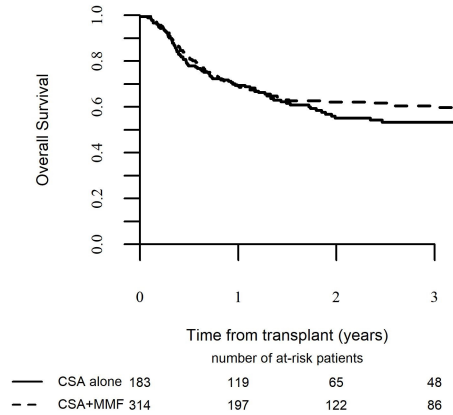
RI



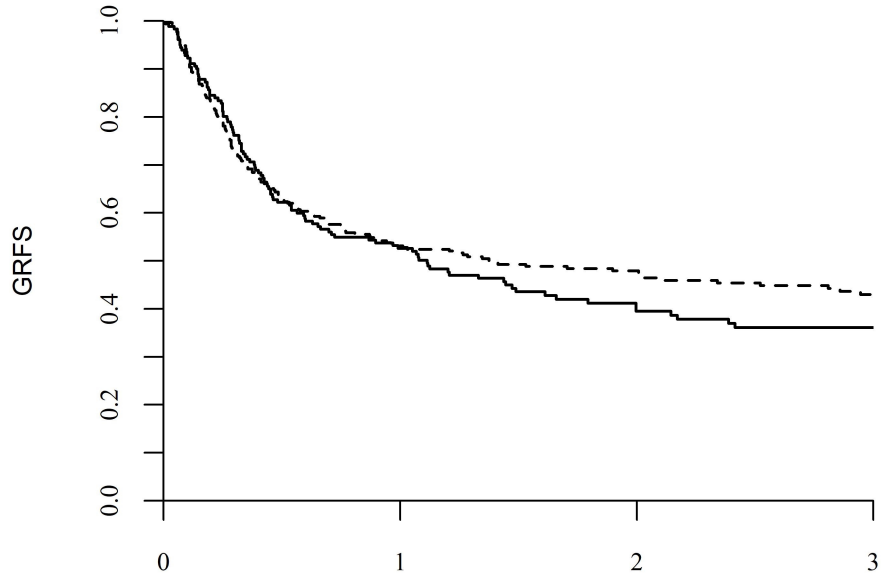
LFS



OS



GRFS



Time from transplant (years)

number of at-risk patients

| | | | | | |
|---------|-----------|-----|-----|----|----|
| — | CSA alone | 181 | 90 | 47 | 35 |
| - - - - | CSA+MMF | 312 | 152 | 97 | 67 |

Supplemental table1. Univariate Analysis

| | 2 years | | | | | 100 days | | 2 years | |
|----------------------|-------------|-------------|-------------|-------------|-------------|------------------|-------------------|--------------|------------------------|
| | RI | NRM | LFS | OS | GRFS | acute GvHD II-IV | acute GvHD III-IV | chronic GVHD | extensive chronic GvHD |
| CSA alone | 26% [20-33] | 21% [16-28] | 52% [45-60] | 55% [47-63] | 40% [32-47] | 27% [21-33] | 9% [6-14] | 38% [31-45] | 17% [11-23] |
| CSA+MMF | 24% [19-29] | 18% [14-22] | 59% [53-64] | 62% [56-68] | 48% [42-54] | 33% [27-38] | 11% [8-14] | 33% [28-39] | 15% [11-19] |
| P value | 0.89 | 0.52 | 0.55 | 0.67 | 0.37 | 0.25 | 0.60 | 0.26 | 0.49 |
| age<59.6y | 24% [19-29] | 17% [13-22] | 59% [52-65] | 62% [55-68] | 48% [41-54] | 29% [23-35] | 9% [6-13] | 39% [32-45] | 16% [12-21] |
| age>=59.6 y | 25% [20-31] | 21% [16-26] | 54% [47-60] | 58% [51-64] | 42% [35-49] | 32% [26-38] | 11% [8-16] | 32% [26-38] | 14% [10-19] |
| P value | 0.84 | 0.31 | 0.31 | 0.15 | 0.49 | 0.53 | 0.32 | 0.04 | 0.25 |
| Year< 2014 | 20% [15-26] | 22% [17-28] | 58% [51-65] | 61% [54-68] | 47% [40-54] | 29% [23-36] | 9% [6-14] | 37% [30-44] | 16% [11-21] |
| Year>=2014 | 28% [22-33] | 17% [13-22] | 55% [49-62] | 59% [53-65] | 43% [37-49] | 31% [26-37] | 11% [8-15] | 34% [28-39] | 15% [11-20] |
| P value | 0.10 | 0.15 | 0.65 | 0.91 | 0.25 | 0.72 | 0.71 | 0.35 | 0.96 |
| CR1 | 23% [19-27] | 19% [16-23] | 57% [53-62] | 61% [56-66] | 45% [40-50] | 32% [27-36] | 11% [8-14] | 36% [31-41] | 15% [12-19] |
| CR2 | 31% [21-42] | 19% [11-28] | 50% [39-62] | 53% [41-64] | 43% [32-55] | 24% [15-34] | 8% [3-15] | 32% [21-43] | 15% [8-23] |
| P value | 0.21 | 0.82 | 0.29 | 0.20 | 0.79 | 0.15 | 0.39 | 0.54 | 0.71 |
| Cytogenetic good | 27% [12-45] | 4% [0-19] | 68% [50-87] | 67% [48-86] | 55% [36-75] | 22% [9-39] | 4% [0-17] | 39% [19-58] | 13% [3-30] |
| intermediate | 22% [17-27] | 19% [15-24] | 59% [53-64] | 62% [57-68] | 46% [40-51] | 31% [26-36] | 12% [8-15] | 39% [34-45] | 17% [13-22] |
| poor | 37% [26-47] | 15% [8-24] | 48% [37-59] | 50% [38-62] | 39% [28-50] | 33% [23-43] | 9% [4-16] | 24% [16-34] | 12% [6-20] |
| P value | 0.07 | 0.04 | 0.17 | 0.15 | 0.54 | 0.56 | 0.44 | 0.02 | 0.35 |
| PS <90 | 23% [16-31] | 17% [11-24] | 60% [52-69] | 62% [53-70] | 47% [39-56] | 32% [24-40] | 12% [7-18] | 37% [28-45] | 16% [10-23] |
| PS>=90 | 25% [20-30] | 21% [16-26] | 54% [49-60] | 59% [53-64] | 45% [39-50] | 30% [25-35] | 10% [7-14] | 35% [30-40] | 14% [10-18] |
| P value | 0.16 | 0.67 | 0.11 | 0.28 | 0.27 | 0.79 | 0.71 | 0.60 | 0.57 |
| BM | 25% [8-46] | 18% [5-36] | 57% [36-79] | 57% [35-79] | 46% [24-69] | 17% [5-34] | 4% [0-18] | 31% [13-51] | 6% [0-27] |
| PBSC | 25% [21-29] | 19% [16-23] | 56% [52-61] | 59% [55-64] | 45% [40-49] | 31% [27-35] | 11% [8-13] | 35% [31-40] | 16% [13-19] |
| P value | 0.89 | 0.79 | 0.68 | 0.72 | 0.39 | 0.25 | 0.72 | 0.59 | 0.09 |
| Male | 23% [18-28] | 22% [17-28] | 55% [49-61] | 58% [51-64] | 41% [34-47] | 33% [27-38] | 10% [7-14] | 37% [31-43] | 19% [14-24] |
| Female | 27% [21-33] | 15% [11-21] | 58% [51-65] | 62% [55-68] | 50% [43-56] | 28% [22-33] | 11% [7-15] | 32% [26-39] | 11% [8-16] |
| P value | 0.05 | 0.03 | 0.90 | 0.86 | 0.40 | 0.11 | 0.93 | 0.24 | 0.12 |
| male donor | 25% [21-30] | 18% [14-22] | 57% [51-63] | 59% [53-65] | 44% [39-49] | 28% [24-33] | 9% [6-13] | 34% [29-40] | 16% [12-21] |
| female donor | 23% [17-30] | 22% [16-29] | 55% [47-62] | 60% [53-68] | 45% [38-53] | 35% [28-42] | 12% [7-17] | 38% [30-45] | 14% [9-21] |
| P value | 0.63 | 0.14 | 0.44 | 0.59 | 0.88 | 0.06 | 0.31 | 0.61 | 0.75 |
| no female to male MM | 24% [20-29] | 19% [15-23] | 57% [52-62] | 59% [55-65] | 46% [41-51] | 29% [25-34] | 10% [7-13] | 34% [30-39] | 15% [12-19] |
| female to male MM | 25% [16-36] | 23% [14-34] | 51% [39-63] | 59% [48-71] | 39% [27-50] | 37% [26-48] | 12% [6-21] | 42% [30-54] | 16% [8-27] |

| | | | | | | | | | |
|---------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-------------|-------------|
| P value | 0.69 | 0.14 | 0.41 | 0.65 | 0.38 | 0.07 | 0.36 | 0.21 | 0.83 |
| Pat. CMV neg. | 27% [21-34] | 16% [11-21] | 57% [50-64] | 62% [55-69] | 46% [39-53] | 25% [19-32] | 9% [6-14] | 30% [24-37] | 13% [9-19] |
| Pat. CMV pos | 23% [18-28] | 21% [16-26] | 56% [50-62] | 58% [52-64] | 44% [38-50] | 34% [28-39] | 11% [7-14] | 38% [33-44] | 17% [13-22] |
| P value | 0.50 | 0.19 | 0.75 | 0.26 | 0.37 | 0.08 | 0.83 | 0.07 | 0.15 |
| Don. CMV neg. | 22% [17-27] | 14% [11-18] | 64% [58-69] | 67% [61-72] | 53% [47-59] | 28% [23-33] | 8% [6-12] | 34% [28-39] | 13% [9-17] |
| Don. CMV pos | 28% [21-35] | 27% [21-34] | 45% [37-53] | 48% [41-56] | 32% [25-39] | 35% [28-42] | 13% [9-18] | 38% [31-45] | 21% [15-27] |
| P value | 0.25 | 0.0003 | 0.0001 | <0.0001 | <0.0001 | 0.07 | 0.12 | 0.25 | 0.02 |

Abbreviations: CR, complete remission; CsA, cyclosporine A; MMF, mycophenolate mofetil; PS, performance status ; BM, bone marrow; PBSC, peripheral blood stem cell; CMV, cytomegalovirus; MM, mismatch; RI, relapse incidence ; NRM, non-relapse mortality; LFS, leukemia free survival, OS, overall survival; GvHD, graft-versus-host disease; GRFS, GvHD free ,relapse-free survival

Table 2. Multivariate analysis

| | RI | | NRM | | LFS | | OS | | GRFS | | Acute GvHD II-IV | | chronic GvHD | |
|----------------------------|------------------|---------|-------------------|---------|------------------|---------|------------------|---------|-------------------|---------|------------------|---------|------------------|---------|
| | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| CSA+MMF versus CSA alone | 0.63 (0.37-1.06) | 0.08 | 0.83 (0.515-1.33) | 0.43 | 0.74 (0.51-1.08) | 0.12 | 0.84 (0.56-1.24) | 0.37 | 0.80 (0.586-1.08) | 0.14 | 1.18 (0.79-1.78) | 0.41 | 0.79 (0.53-1.17) | 0.25 |
| Good Cytogenetics | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | | 1 | |
| Intermediate | 0.81 (0.35-1.89) | 0.63 | 1.87 (0.43-8.09) | 0.40 | 1.08 (0.52-2.22) | 0.84 | 1.03 (0.49-2.13) | 0.95 | 1.01 (0.54-1.89) | 0.97 | 1.11 (0.43-2.85) | 0.83 | 1.06 (0.49-2.27) | 0.89 |
| adverse | 1.58 (0.62-3.98) | 0.34 | 1.32 (0.27-6.44) | 0.73 | 1.38 (0.63-3.03) | 0.43 | 1.28 (0.57-2.86) | 0.55 | 1.12 (0.56-2.24) | 0.75 | 1.12 (0.40-3.12) | 0.83 | 0.55 (0.23-1.36) | 0.19 |
| age (per 10y) | 0.89 (0.73-1.08) | 0.25 | 1.39 (1.05-1.85) | 0.02 | 1.05 (0.89-1.24) | 0.54 | 1.13 (0.96-1.35) | 0.17 | 1.03 (0.89-1.19) | 0.69 | 1.15 (0.94-1.4) | 0.17 | 0.91 (0.77-1.07) | 0.25 |
| CR2 versus CR1 | 1.26 (0.76-2.1) | 0.38 | 0.97 (0.53-1.81) | 0.94 | 1.11 (0.75-1.65) | 0.60 | 1.13 (0.75-1.72) | 0.55 | 0.98 (0.68-1.4) | 0.91 | 0.72 (0.42-1.24) | 0.24 | 0.85 (0.54-1.34) | 0.49 |
| KPS>=90 versus KPS<90 | 1.2 (0.76-1.92) | 0.44 | 1.2 (0.744-1.94) | 0.45 | 1.23 (0.88-1.73) | 0.23 | 1.19 (0.84-1.69) | 0.34 | 1.15 (0.86-1.53) | 0.35 | 0.93 (0.64-1.36) | 0.72 | 0.98 (0.68-1.41) | 0.90 |
| PBSC vs BM | 1.5 (0.53-4.28) | 0.45 | 0.95 (0.34-2.66) | 0.92 | 1.26 (0.60-2.65) | 0.54 | 1.15 (0.52-2.53) | 0.74 | 1.55 (0.78-3.09) | 0.21 | 1.29 (0.52-3.23) | 0.59 | 1.83 (0.78-4.28) | 0.16 |
| Female to male MM vs other | 0.76 (0.42-1.36) | 0.35 | 1.26 (0.73-2.16) | 0.41 | 0.97 (0.65-1.45) | 0.89 | 0.95 (0.62-1.44) | 0.79 | 0.97 (0.68-1.4) | 0.89 | 1.5 (0.95-2.36) | 0.08 | 1.49 (0.96-2.31) | 0.07 |
| Patient CMV pos | 0.67 (0.45-1.02) | 0.06 | 1.06 (0.67-1.68) | 0.79 | 0.83 (0.61-1.12) | 0.22 | 0.95 (0.69-1.31) | 0.75 | 0.90 (0.68-1.19) | 0.46 | 1.22 (0.84-1.77) | 0.29 | 1.28 (0.9-1.82) | 0.17 |
| Donor CMV pos | 1.44 (0.97-2.15) | 0.07 | 2.03 (1.31-3.14) | 0.001 | 1.69 (1.26-2.27) | <0.001 | 1.66 (1.22-2.26) | 0.001 | 1.75 (1.34-2.28) | <0.001 | 1.26 (0.88-1.8) | 0.21 | 1.44 (1.02-2.04) | 0.04 |
| centre (frailty) | | <0.001 | | 0.24 | | 0.006 | | 0.006 | | 0.13 | | 0.21 | | 0.06 |

Abbreviations: CR, complete remission; CsA, cyclosporine A; MMF, mycophenolate mofetil; KPS, Karnofsky performance status ; BM, bone marrow; PBSC, peripheral blood stem cells; CMV, cytomegalovirus; MM, mismatch; RI, relapse incidence ; NRM, non-relapse mortality; LFS, leukemia free survival, OS, overall survival; GvHD, graft-versus-host disease; GRFS, GvHD free, relapse-free survival.