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Impact of Cyclosporine-A Concentration on Acute Graft-versus-Host Disease Incidence after Haploidentical Hematopoietic Cell Transplantation

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Running title: Role of cyclosporine-A in Haplo-HCT

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Abstract

Objectives: This retrospective study analyzed the impact of early cyclosporine-A (CsA) initiation (day – 3) on the risk of acute graft-versus-host disease (aGvHD) after haploidentical hematopoietic cell transplantation (Haplo-HCT) using post-transplant cyclophosphamide

Methods: Sixty-one consecutives patients who underwent Haplo-HCT were analyzed.

Results: At day +180, the cumulative incidences of grade II-IV and grade III-IV aGvHD were 39% and 18%, respectively. Patients having a lowest CsA concentration (<301 ng/mL; the cut-off value used to segregate the patients between low and high CsA concentrations) in the first week after Haplo-HCT had a significantly higher risk of grade II-IV aGvHD (P= .02), severe grade III-IV aGvHD (P = .03), cGvHD (P= .02) and extensive cGvHD (P= .04). In multivariate analysis, a higher CsA concentration (≥301 ng/mL) during the first week following Haplo-HCT was the only parameter significantly associated with a reduced risk of grade II-IV and grade III-IV aGvHD (RR=.21; P=.049 and RR<0.001; P<.0001, respectively). We find no correlation between CsA concentration and relapse, non-relapse mortality, progression free survival, GvHD-free and progression free survival or overall survival.

Conclusions: CsA could be initiated early before Haplo-HCT with achievement of high CsA concentration to reduce the risk of aGvHD without any detrimental effect on relapse.

Key words:

- Cyclosprorine-A
- Haploidentical stem cell transplantation
- Post-transplant cyclophosphamide
- Acute graft-versus-host disease.

Introduction

Allogeneic hematopoietic stem cell transplantation using a related haploidentical donor (Haplo-HCT) is an alternative option for patients lacking a fully matched sibling or a well matched unrelated donor [1]. However, Haplo-HCT is limited by the immunologic recognition and destruction of host tissues due to the number of HLA mismatches and termed graft-versus-host disease (GvHD). Therefore, both in its acute and chronic forms (GvHD is one the main life-threatening complications after Haplo-HCT [2]. However, new strategies have been developed for GvHD prophylaxis post Haplo-HCT, such as the use of high dose anti-thymocyte globulin (ATG) - the so called GIAC protocol - or the use of post-transplant high-dose cyclophosphamide (PTCy) [3]. In particular the use of high-dose PTCy (50 mg/kg days +3 and +4) has been developed as an effective GvHD prophylaxis by Luznik *et al*. [4], based on the rationale that cyclophosphamide is non-toxic to hematopoietic stem cells and can selectively deplete the alloreactive T cells. In this first report, PTCy was combined with mycophenolate mofetil (MMF) and tacrolimus, which were initiated after completion of PTCy to avoid blocking Cy-induced tolerance [4,5]. Bacigalupo *et al*. slightly modified the GvHD prophylaxis with PTCy (50 mg/kg days +3 and +5) together with CsA and MMF started at day 0 and day +1 respectively, resulting in a 4% incidence of grade III-IV acute GvHD (aGvHD) with bone-marrow (BM) grafts [6]. However, use of peripheral blood stem cells grafts (PBSC) in the PTCy setting is associated with an increased risk of aGvHD compared to BM grafts [7] highlighting the need to reinforce GvHD prophylaxis in those patients. Therefore, in our center when using PBSC grafts for Haplo-HCT with PTCy, we decided to incorporate a low dose of ATG in the conditioning regimen and initiated CsA earlier at day -3 before transplant, to lower the risk of GvHD associated with PBSC [7].

The importance of achieving a high CsA concentration early after transplant to lower the incidence of aGvHD has been clearly demonstrated [8-11]. However, all the studies have been performed outside of the Haplo-HCT setting and the exact role of an early high CsA concentration on aGvHD remains to be determined. Furthermore, whether to start CsA before or after PTCy still remains controversial. Thus, while it was thought that administration of a calcineurin inhibitor before PTCy could interfere with Cy induced tolerance, initiation of CsA before PTCy has been reported to be associated with a very low incidence of aGvHD without suppressing the PTCy effect [6].

With this background, we decided to retrospectively analyze 61 consecutive patients who underwent Haplo-HCT with PBSC grafts and PTCy with the aim of assessing the impact of early initiation of CsA (before PTCy), and the correlation between early CsA concentration and the onset of aGvHD.

Patients and Methods

Patients

Sixty-one patients who underwent Haplo-HCT for hematological malignancies between October 2013 and August 2017 at the University Hospital of Saint-Antoine (AP-HP, Paris, France) were included in this retrospective single-center study. The primary endpoint of the study was to determine the impact of the serum CsA concentration on the risk of grade II-IV aGvHD. For the purpose of this analysis, all patients who received Haplo-HCT with PTCy and a PBSC graft were included. Written informed consent was obtained from each patient and donor. This study was approved by the hospital's institutional review board, and the local ethics committee. All patients had no HLA-identical sibling or unrelated donor available or a suitable unrelated donor was not available within the appropriate time frame for the patient's malignancy and clinical circumstances. HLA typing was performed according to the recommendations of the European Federation for Immunogenetics (EFI) Histocompatibility Laboratory standards during the study period. Molecular high-resolution typing of HLA-A, -B, -C, -DQB1, and -DRB1 alleles was performed for each patient and donor.

Transplantation Procedure

All patients received the preparative regimen as inpatients in private rooms and remained hospitalized until hematopoietic and clinical recovery. They all received granulocyte-colony stimulating factor mobilized PBSC as grafts and post-transplantation immunosuppression with CsA and MMF. CsA was administered at a dose of 3mg/kg by continuous intravenous infusion starting from day -3 and changed to twice daily oral dosing as soon as tolerated. MMF was administered at a fixed oral dose of 2g per day starting from day +5 without

adjustment. In the absence of GvHD, MMF and CsA were tapered over 4 weeks starting from day +60 and day +90, respectively. Of note, supportive care was the same for all patients during the whole study period. CMV infection management was also homogeneous. All blood products were filtered, irradiated and CMV screened. In the first 100 days post Haplo-HCT, patients were assessed at least once per week for CMV reactivation by PCR assay to initiate preemptive ganciclovir therapy.

CsA Concentration Monitoring and Diagnosis of GvHD

CsA blood trough concentrations were monitored 3 times per week during the intravenous treatment and at least once per week after switch to oral dosing. Trough levels of CsA were assessed by radioimmunoassay (RIA) using commercially available kits (Immunotech, Beckman-Coulter, France) according to the manufacturer's procedures. Blood samples were collected early in the morning. For the purpose of this analysis, the mean weekly concentration of CsA was calculated for each patient using the different concentrations measured during a defined week. CsA doses were adjusted to achieve blood levels of between 200 and 300 ng/mL and to prevent renal dysfunction. Acute GvHD was diagnosed and graded according to the revised Glucksberg criteria [12] and chronic GvHD (cGvHD) was diagnosed and graded according to the Seattle standard criteria [13]. Time to neutrophil recovery was defined as the first of 3 consecutive days in which the absolute neutrophil count exceeded 0.5×10^9/L, and platelet recovery as the first of 5 consecutive days with a platelet count above 50×10^9/L without the need for platelet transfusion.

Statistical Analysis

Comparison between or patients who experienced no or grade I acute GvHD and patients with grade II-IV aGvHD was carried out using the chi-squared test for categorical variables, and the t-test for continuous data. The diagnostic values of the CsA concentration were assessed at week 1, 2, 3 and 4 after Haplo-HCT by constructing ROC curves and then for each one, calculating the area under the curve (AUC). The cumulative incidence of aGvHD, cGvHD, relapse, and non-relapse mortality (NRM) were estimated and groups were compared using Gray's test. Relapse was defined as a competitive risk for NRM, and vice versa. Progression-free survival (PFS) was calculated from the date of Haplo-HCT until the time to relapse or progression. Overall survival (OS) was calculated from the date of Haplo-HCT until the time of death or the last observation if a patient remained alive. Refined GvHD-free and progression-free survival (GPFS) was defined as a combination of survival with no evidence of relapse/progression, grade III to IV aGvHD, and extensive cGvHD [14]. Probabilities of PFS, GPFS and OS were estimated using the Kaplan–Meier method and groups were compared using the Log-rank test. Fine-Gray logistic regression analyses were performed with relevant variables to identify independent risk factors for grade II-IV aGvHD, grade III-IV aGvHD, cGvHD and extensive cGvHD development. All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing; version 3.5.0) [15].

Results

Characteristics of Patients, Donors and Transplantations

Patient, donor, and transplant characteristics are summarized in **Table 1**. The median age was 53 years (range, 15-72), with 16 male patients (26%) receiving a graft from a female donor. Diagnoses were myeloid malignancies (64 %) or lymphoid malignancies (36%). According to the Disease Risk Index, patients were considered as low-risk, intermediate-risk, high-risk or very-high-risk (8%, 56%, 31% and 5% respectively) [16]. Twenty-five patients (41%) with refractory disease received a sequential conditioning regimen based on thiotepa 5 to 10 mg/kg, etoposide 400 mg/m^2, and cyclophosphamide 1600 mg/m^2 between days -15 to -9, followed by, after a 3-day rest, reduced intensity conditioning (RIC) with fludarabine 150 mg/m^2 and i.v. busulfan 6.4 mg/kg on days -6 to -1 [17], while the remaining 36 patients (59%) received a reduced-intensity/toxicity conditioning (RIC/RTC) regimen based on 150 mg/m^2 fludarabine, 2 to 3 days of 3.2 mg/kg/d busulfan and thiotepa. Fifty-one patients (83%) received ATG as part of the conditioning regimen. All patients received standard PTCy, 9 (15%) at day +3 and 52(85%) at day +3 and day +5. Median follow-up among surviving patients was 21 months (range, 13-53) (**Table 2**).

CsA Concentration and aGvHD

Median concentrations of CsA in the blood at 1, 2, 3, and 4 weeks after Haplo-HCT were 272 ng/mL (range, 114-911), 296 ng/mL (range, 132-516), 251 ng/mL (range, 111-485), and 246 ng/mL (range, 36-375), respectively (**Figure 1**). ROC curve analysis revealed that CsA concentration was an accurate discriminator of the risk of grade II-IV aGvHD. The cut-off values providing the best balance between sensitivity and specificity were 301ng/ml,

297ng/ml, 261ng/ml and 238ng/ml at 1, 2, 3, and 4 weeks after Haplo-HCT, respectively. At day +180, the cumulative incidences of grade II-IV and grade III-IV aGvHD were 39% and 18%, respectively. Univariate analysis of risk factors for grade II-IV aGvHD is shown in **Table 1**. Patients having the lowest CsA concentration in the first week after Haplo-HCT had a significantly higher risk of grade II-IV aGvHD (P= .02) (**Table 2, Figure 2A**). Moreover, there was a significant association between severe grade III-IV aGvHD and CsA concentration in the first week after Haplo-HCT (P = .03) (**Table 2, Figure 2B**). In contrast, we did not find any correlation between CsA concentration beyond the first week and the risk of aGvHD. In multivariate logistic regression analyses (**Table 3**), a higher CsA concentration (≥ 301 ng/ mL; the cut-off value used to segregate the patients between low and high CsA concentrations) during the first week following Haplo-HCT was the only independent parameter significantly associated with a reduced risk of grade II-IV and grade III-IV aGvHD (RR .21; 95% CI, 0.05-0.99, P = .049; and RR < .001; 95% CI, 0.000007-0.00005, P < .0001, respectively).

Engraftment and Clinical Outcomes

Engraftment and clinical outcome characteristics for the whole cohort and according to the CsA level in the first week are summarized in **Table 2**. Median time for neutrophil and platelet engraftment) was 18 days (range, 13 to 35) and 26 days (range, 14 to 88) , respectively. Three secondary graft failures occurred after Haplo-HCT. The cumulative incidence (CI) of cGvHD, extensive cGvHD and relapse was 41%, 19% and 35% at 18 months after Haplo-HCT, respectively. At 18 months after the transplant, the OS, PFS and GPFS rates were 60%, 55% and 48% respectively. Patients having the lowest CsA concentration in the first week after Haplo-HCT had a significantly higher risk of cGvHD (P= .02) and of extensive

cGvHD (P= .04). In multivariate logistic regression analysis, no parameters were associated with an increased risk of cGVHD (**Table 3**).

We find no statistically significant correlation in terms of relapse incidence, NRM, PFS, GPFS or OS between patients having the highest CsA concentration in the first week after Haplo-HCT, compared to patients with a lower CsA concentration (**Figure 3**).

Discussion

Thirty years ago, the Seattle group demonstrated that a low CsA concentration increases the risk of aGvHD, and that concentrations should be monitored in BM transplant recipients [8]. In this study, Yee et al. reported a relative risk of 0.7 for every increase of 100 ng/mL of the CsA concentration [8]. This inverse relation between trough CsA levels and incidence of GvHD in patients that received a bone marrow graft was further confirmed in the early 1990s [11,18,19]. Our group found a similar correlation in patients transplanted from matched related or unrelated donors and PBSC graft [11]. However, data regarding the impact of CsA level on GvHD in the Haplo-HCT setting are scarce. In our study, we evaluated the impact of serum CsA concentration on the incidence of aGvHD in a homogenous group of adult patients undergoing Haplo-HCT with PBSC and PTCy as GvHD prophylaxis given in combination with ATG, CsA and MMF.

Due to the mechanism by which PTCy aids in preventing GvHD after Haplo-HCT, which involves in vivo selective destruction of alloreactive T cells, induction of tolerance, and intra-thymic clonal deletion of alloreactive T lymphocytes [20], it was thought that early initiation of CsA before Haplo-HCT would abolish the PTCy effect. Our strategy was associated with day +180 cumulative incidences of grade II-IV and grade III-IV aGvHD of 39% and 18%, respectively. These findings are comparable with the incidences found by Ruggeri et al. [7] (38% and 14%, respectively) and Castagna et al. [21] (38% and 12%, respectively) in patients receiving PBSC Haplo-HCT with PTCy and calcineurin inhibitor initiation at day +5. Therefore, early introduction of CsA is not detrimental [21]. On the contrary,[8-11], we observed that achievement of a high concentration of CsA at time of engraftment, before PTCy administration, was associated with a lower incidence of aGVHD, being 18% for grade II-IV

and 0% for grade III-IV, at day +180. These findings were also observed in the setting of allogeneic hematopoietic stem cell transplantation using a well matched-related or matched-unrelated donors [8,11].

In addition, we find that an achievement of a high CsA concentration during the first week after transplant, resulted in a significant decrease of the CI of cGvHD and extensive cGvHD, with a CI at 18 months of 16% and 0% respectively. This result compares very favorably with the study by Ruggeri et al. that reported a CI of 32% and 10% respectively.

One could question the impact of achievement of a high CsA concentration on the risk of relapse. However, in univariate analysis, we did not find any impact on the CI of relapse. Another concern may be the deleterious impact of a high CsA concentration on renal function. Given the retrospective nature of this study, we were not able to analyze renal function, however we do not report any long-term renal side effect in the high CsA concentration group of patients.

Besides PTCy, the impact of early CsA concentration was recently investigated in the context of T-cell replete Haplo-HCT using the GIAC protocol[22]. Similar to our findings, the authors report that achievement of a high CsA concentration after haplo-HCT was associated with a reduced incidence of aGvHD [22].

While our study may underestimate unmeasured factors that have not been considered, a limitation when conducting retrospective studies, we find that early introduction and monitoring of CsA in Haplo-HCT with PTCy GvHD prophylaxis can improve the clinical outcome by reducing the risk of grade II-IV and grade III-IV aGvHD in patients receiving PBSC grafts. Although one must acknowledge that clinical obstacles such as renal failure, drug

interactions, and pharmacodynamics of CsA may preclude early achievement of high CsA levels, we conclude that data from the current study indicate that CsA should be initiated before PTCy with the aim of achieving a high CsA trough blood concentration during the early post-Haplo-HCT to prevent the onset of aGvHD. Inadequate or insufficient early exposures to CsA following Haplo-HCT with PTCy GvHD prophylaxis can be a serious risk for developing severe aGvHD and a high CsA target concentration remains an effective tool to prevent the onset of this event.

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Authorship Contributions

NS, MM and FM designed the study, NS collected the data, EB, GB, RD, FG, AR, MM and FM recruited the patients, NS and FM performed the statistical analysis and, NS, MM and FM prepared the manuscript for publication. All authors analyzed the data, reviewed the manuscript, and agreed to its submission for publication.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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Table 1. Univariate analysis of risk factors for grade II-IV aGvHD

Characteristic	Patients with no or Grade I aGvHD n=43; (%)	Patients with Grade II-IV aGvHD n=18; (%)	*P* value
Patient age, (yrs) median (range)	54 (15-72)	49 (16-66)	.14
Patient age > 60 yrs	15 (35)	4 (22)	.38
Patient gender			
Male	28 (65)	11 (61)	.77
Female	15 (35)	7 (39)	
Donor gender			
Female to male	11 (26)	5 (28)	1
ABO mismatch	24 (56)	7 (39)	.27
CMV serologic status			
Seronegative donor-recipient pair	3 (7)	3 (17)	.34
Diagnosis			
Myeloid malignancies	28 (65)	11 (61)	.77
Lymphoid malignancies	15 (35)	7 (39)	
Disease Risk Index			
Low-Intermediate	27 (63)	12 (67)	1
High-Very High	16 (37)	6 (33)	
Conditioning regimen category			
RIC/RTC	25 (58)	11 (61)	1
Sequential conditioning	18 (42)	7 (39)	
ATG			
Without	5 (12)	5 (28)	.14
With	38 (88)	13 (72)	
Post-transplant cyclophosphamide			
D+3	8 (19)	1 (6)	.25
D+3/D+5	35 (81)	17 (94)	
CsA blood concentrations during the first week after Haplo-HCT, median (ng/ml; range)			
< 301 ng/ml	25 (58)	16 (89)	**.03**
≥ 301 ng/ml	18 (42)	2 (11)	
CsA blood concentrations during the second week after Haplo-HCT, median (ng/ml; range)			
< 297 ng/ml	23 (54)	8 (44)	.58
≥ 297 ng/ml	20 (46)	10 (56)	
CsA blood concentrations during the third week after Haplo-HCT, median (ng/ml; range)			
< 261 ng/ml	25 (58)	9 (50)	.59
≥ 261 ng/ml	18 (42)	9 (50)	
CsA blood concentrations during the fourth week after Haplo-HCT, median (ng/ml; range)			
< 238 ng/ml	20 (46)	10 (56)	.58
≥ 238 ng/ml	23 (54)	8 (44)	

Abbreviations: CMV, cytomegalovirus; ATG, antithymo-globulins; CsA, cyclosporine A; Haplo-HCT, haploidentical hematopoietic stem cell transplantation; RIC, reduced-intensity conditioning; RTC; reduced-toxicity conditioning. * Myeloid malignancies: 31 acute myeloid leukemia, 4 myelodysplastic syndrome, 3 myeloproliferative syndrome and 1 MDS/MPS; lymphoid malignancies: 8 acute lymphoblastic leukemia, 9 non-Hodgkin's lymphoma and 5 Hodgkin's disease. Bold denotes statistical significance.

374 **Table 2. Engraftment and clinical outcomes after Haplo-HCT**

Characteristic	All patients (n=61)	CsA < 301 ng/ml (n=41)	CsA ≥ 301 ng/ml (n=20)	*P* value
Graft failure	3 (5)	2 (5)	1 (5)	1
Median time for neutrophil > 0.5 x 10^9/L (range), days	18 (13-35)	17 (13-31)	18 (13-35)	.66
Median time for platelets > 50 x 10^9/L (range), days	26 (14-88)	24 (12-88)	29 (13-55)	.71
aGvHD incidence at day +180, % (95%CI)	63 (47-74)	66 (46-78)	59 (26-77)	.38
Grade II-IV	39 (22-52)	49 (27-64)	18 (0-39)	**.02**
Grade III-IV	18 (7-31)	26 (8-41)	0	**.03**
cGvHD incidence at month 18, % (95%CI)	41 (22-56)	55 (28-72)	16 (0-35)	**.02**
Extensive	19 (1-33)	31 (2-52)	0	**.04**
Non-relapse mortality at month 18, % (95%CI)	20 (9-30)	23 (8-36)	15 (0-29)	.50
Relapse incidence at month 18, % (95%CI)	35 (18-48)	32 (11-48)	44 (9-65)	.43
Progression-free survival at month 18, % (95%CI)	55 (42-67)	53 (36-67)	60 (35-77)	.87
GPFS at month 18, % (95%CI)	48 (34-60)	42 (26-57)	60 (35-77)	.39
Overall survival at month 18, % (95%CI)	60 (46-71)	58 (41-72)	64 (39-81)	.67
Median follow-up, months (range)	21 (10-53)	30 (10-53)	19 (13-52)	.64

375 Abbreviations: aGvHD, acute graft-versus-host disease; CI, confidence interval; GPFS, graft-versus-host
376 disease and progression-free survival; cGvHD, chronic graft-versus-host disease; Haplo-HCT,
377 haploidentical hematopoietic stem cell transplantation. Bold denotes statistical significance.

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382 **Table 3. Multivariate analysis of acute GvHD, chronic GvHD and relapse risk factors**

Outcome	Hazard ratio (95% CI)	P value
Grade II-IV acute GvHD		
Age > 60 vs <60 years	0.68 (0.22-2.05)	.49
ATG vs no ATG	0.36 (0.12-1.09)	.07
CsA ≥ 301 ng/ml vs CsA < 301 ng/ml	0.21 (0.05-0.99)	**.049**
CMV donor/recipient negative vs others	0.98 (0.19-4.97)	.98
Female donor to male recipient vs others	0.96 (0.31-2.99)	.95
Grade III-IV acute GvHD		
Age > 60 vs <60 years	0.72 (0.13-3.99)	.70
ATG vs no ATG	0.25 (0.05-1.29)	.98
CsA ≥ 301 ng/ml vs CsA < 301 ng/ml	< 0.001 (0.000007-0.00005)	**< .001**
CMV donor/recipient negative vs others	1.29 (0.15-10.9)	.82
Female donor to male recipient vs others	0.86 (0.15-4.92)	.87
Chronic GvHD		
Age > 60 vs <60 years	0.46 (0.09-2.36)	.35
ATG vs no ATG	1.93 (0.38-9.90)	.43
CsA ≥ 301 ng/ml vs CsA < 301 ng/ml	0.31 (0.07-1.44)	.13
CMV donor/recipient negative vs others	3.52 (0.55-22.34)	.18
Female donor to male recipient vs others	2.00 (0.79-5.00)	.14
Relapse incidence		
Age > 60 vs <60 years	2.06 (0.71-6.05)	.18
ATG vs no ATG	0.28 (0.11-0.73)	**.009**
CsA ≥ 301 ng/ml vs CsA < 301 ng/ml	1.69 (0.65-4.38)	.28
RTC vs MAC	0.74 (0.10-5.83)	.78
DRI very-high/high vs low/very-low	6.16 (0.72-53.05)	.10

383 Abbreviations: aGvHD, acute graft-versus-host disease; ATG, antithymoglobulin; CI, confidence interval;
384 CMV, cytomegalovirus; CsA, cyclosporine A; Haplo-HCT, haploidentical hematopoietic stem cell
385 transplantation; MAC, myeloablative conditioning regimen; RTC, reduced-toxicity conditioning regimen.
386 Bold denotes statistical significance.
387
388
389

Figure 1. CsA values at weekly intervals post Haplo-HCT.

Box and whisker plots are displayed, showing the minimum, first quartile, median, third quartile, and maximum. CsA, cyclosporine-A; Haplo-HCT, haploidentical hematopoietic stem cell transplantation.

Figure 2. Cumulative incidence of grade II-IV aGvHD and grade III-IV aGvHD according to CsA concentration during the first week after Haplo-HCT.

Probability of grade II-IV acute GVHD (**2a**) and grade III-IV acute GvHD (**2b**) according to CsA concentration (below or over 301 ng/ml) in the first week after Haplo-HCT. aGvHD, acute graft versus host disease; CsA, cyclosporine-A; Haplo-HCT, haploidentical hematopoietic stem cell transplantation.

Figure 3. Other clinical outcomes according to CsA concentration during the first week after Haplo-HCT.

Cumulative incidence of chronic GvHD (**3a**), relapse (**3b**) and non-relapse mortality (**3c**) according to CsA concentration (below or over 301ng/ml) in the first week after Haplo-HCT. Progression-free survival (**3d**); graft-versus-host-disease and relapse-free survival (**3e**) and overall survival (**3f**) according to CsA concentration (below or over 301ng/ml) in the first week after Haplo-HCT. cGvHD; chronic graft-versus-host disease, CsA, cyclosporine A; Haplo-HCT, haploidentical hematopoietic stem cell transplantation; NRM; non-relapse mortality, PFS, progression-free survival; GPFS, graft-versus-host disease and relapse-free survival; OS, overall survival.

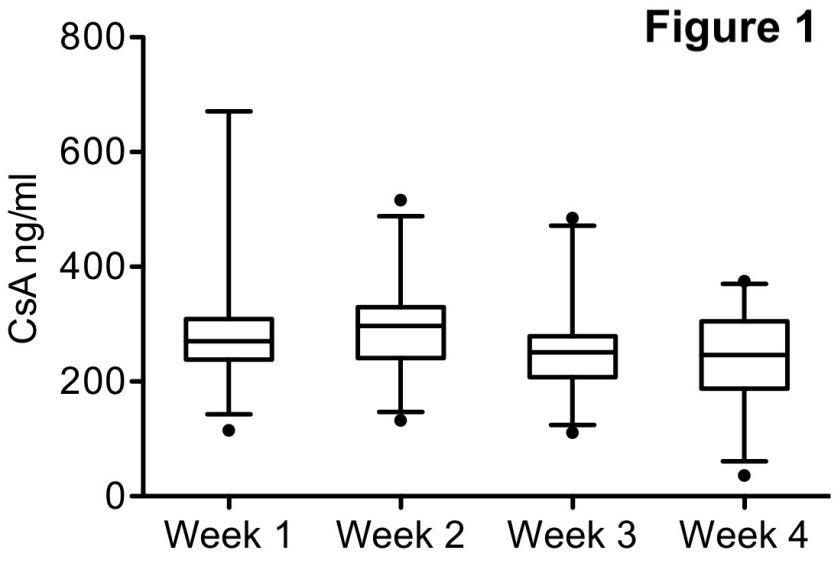

Figure 1

110x72mm (300 x 300 DPI)

Figure 2

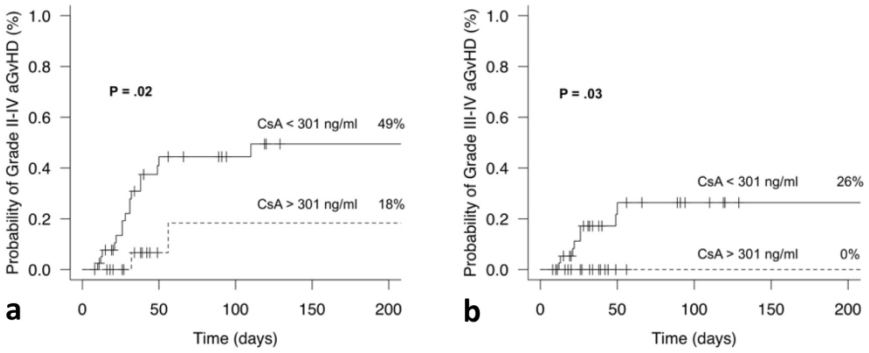

Figure 2

165x85mm (300 x 300 DPI)

Figure 3

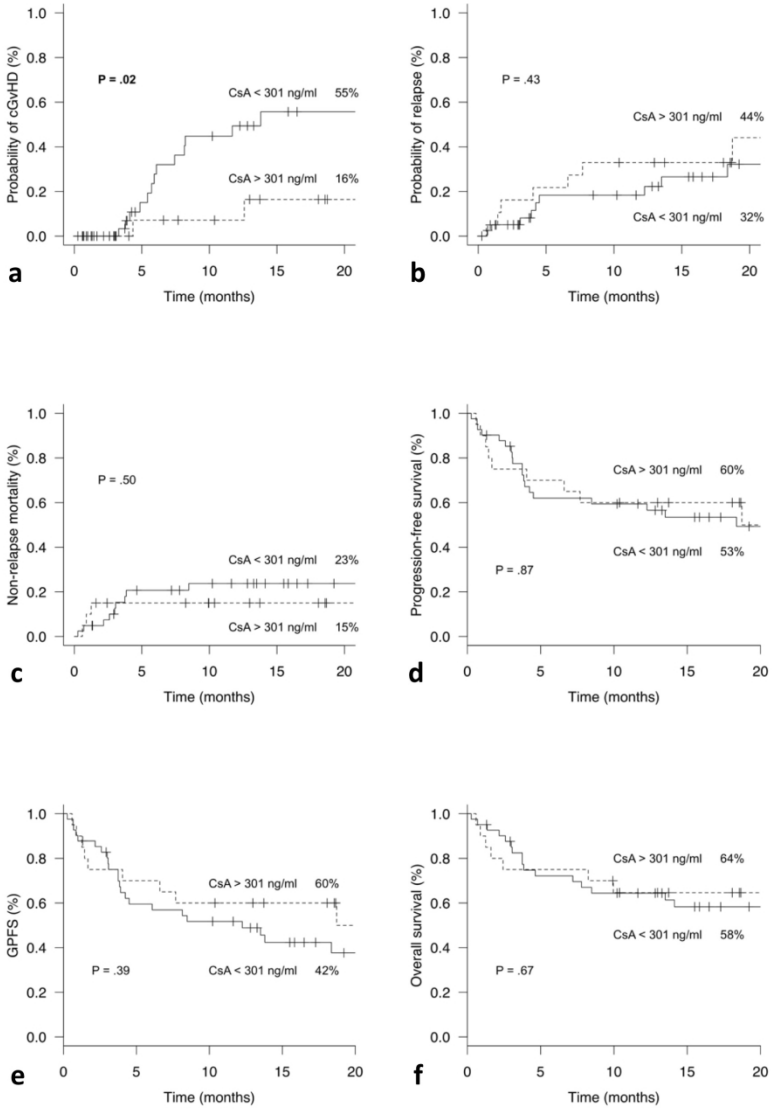

Figure 3

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