

# Randomized study between thymoglobulin and posttransplant cyclophosphamide in patients with chronic myeloid neoplasms undergoing unrelated allogeneic stem cell transplantation

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## Summary

Despite growing evidence on the use of posttransplantation cyclophosphamide (PTCY) in matched unrelated transplantation in acute leukemia patients, prospective evidence to support this type of prophylaxis in myelodysplastic syndrome (MDS), chronic myeloproliferative neoplasms and chronic myeloid leukemia (CML) patients is lacking. In this patient population we conducted a prospective randomized study of PTCY vs thymoglobulin for graft-versus-host disease (GvHD) prophylaxis in the setting of 10/10 HLA-matched unrelated transplantation (NCT02627573, clinicaltrials.gov). The strata for randomization was pretransplant assessment of mortality score. The study was terminated prematurely due to poor recruitment, but 33 patients were enrolled, 17 in the PTCY and 16 in the thymoglobulin group. Median follow up was 29 months. There was no difference between groups in the incidence primary graft failure (12.50% vs 11.8%,  $p=0.9$ ), acute GvHD grade II-IV (23% vs 6%,  $p=0.2$ ), moderate and severe chronic GvHD (25% vs 23%,  $p=0.4$ ) in the thymoglobulin and PTCY arms,

respectively. However there was a significantly higher overall survival (82% vs 30%,  $p=0.0126$ ), event-free survival (61% vs 26%,  $p=0.0335$ ), and GvHD-relapse free survival (61% vs 16%,  $p=0.0072$ ) in the PTCY group due to reduced late infection-related mortality. No differences was observed in terms of toxicity. In conclusion, despite incomplete recruitment, the study created the basis for the use of PTCY in unrelated transplantations from fully matched unrelated donors in CML and MDS. Future studies are required to confirm if there is a benefit of PTCY-based prophylaxis over thymoglobulin.

## Keywords

Posttransplant cyclophosphamide, myelodysplastic syndrome, chronic myeloid leukemia, chronic myeloproliferative neoplasm, matched unrelated donor.

## Introduction

Myelodysplastic syndrome (MDS), chronic myeloproliferative neoplasms (MPN) and chronic myeloid leukemia (CML) comprise about 15% of patients with indication for allogeneic stem cell transplantation (SCT) [1]. Nonetheless SCT in this group of patients is associated with significant non-relapse mortality reaching 26% in advanced chronic myeloid leukemia [2], 32% in myelodysplastic syndrome [3] and 25-36% in various types of MPN [4, 5]. The main reasons of mortality in these diseases are infectious complications, graft-versus-host disease and primary graft failure which is significantly more frequent than in other hematological malignancies [6].

Posttransplant cyclophosphamide (PTCY) is an approach which is gaining popularity for haploidentical (Haplo) and mismatched unrelated donor (MUD) transplantation. This approach in the large retrospective study demonstrated reduced incidence of GvHD, reduced non-relapse mortality and improved GvHD-relapse-free survival (GRFS) compared to *in vivo* T-cell depletion methods both in Haplo and MUD settings [7, 8]. But most of the supportive data describes acute leukemia patients [9] or MDS/MPN patients are combined in the analysis with acute leukemia [10]. Thus there is limited data whether PTCY in the group of chronic myeloid neoplasms provide the same benefit as in acute leukemias. Also there was a concern that in the setting of MDS/CML/MPN PTCy might increase the primary graft failure incidence.

The majority of SCTs in MDS and CML patients are unrelated, because of older age and comorbidities of the related donors and better outcomes after transplantation from a young donor [11]. So we conducted a single-center prospective randomized study in unrelated SCT recipients between the standard approach of GvHD prophylaxis with thymoglobulin and PTCY. The other components of GvHD prophylaxis was the same as well as the conditioning and supportive care.

## Patients and methods

### General parameters of the patients and transplants

The prospective single-center randomized study was conducted in the First Pavlov Medical university. The study was approved by the local Ethical committee and was conducted according to the good clinical practices and Helsinki declaration. All patients signed informed consent to participate in the study and processing of the personal data. The study was registered at clinicaltrials.gov, NCT02627573. The conclusion criteria were the diagnosis of chronic myeloid leukemia or myelodysplastic Syndrome or myeloproliferative neoplasm unclassified or atypical chronic myelogenous leukemia with indications for SCT and presence of 10/10 HLA-matched unrelated donor. The donor and recipient must be identical by the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. Mismatches in these loci were not allowed. Also only patients were included in whom the donor agreed to donate peripheral blood stem cells (PBSC). The exclusion criteria were the presence

of severe concurrent illness, prior history of anaphylaxis to thymoglobulin, moderate or severe cardiac dysfunction, left ventricular ejection fraction <50%, moderate or severe decrease in pulmonary function, FEV1 <70% or DLCO <70% of predicted, respiratory distress at least grade I, severe organ dysfunction: AST or ALT >5 upper normal limits, bilirubin >1.5 upper normal limits, creatinine >2 upper normal limits, creatinine clearance <60 mL/min., uncontrolled bacterial or fungal infection at the time of enrollment, requirement for vasopressor support at the time of enrollment, Karnofsky index <30%, pregnancy, and somatic or psychiatric disorder making the patient unable to sign informed consent. The study during 2015-2019 has enrolled 33 patients: 16 in the thymoglobulin arm and 17 in the PTCY arm. The study was terminated prematurely due to poor recruitment. All recruited patients were included in the analysis. The study group was well balanced with no significant differences in characteristics of patients (Table 1).

### Study procedures

All patients received conditioning with fludarabine 180 mg/m<sup>2</sup> over 6 days and oral busulfan 10 mg/kg over 3 days. Patients in the thymoglobulin group received GvHD prophylaxis with thymoglobulin 2.5 mg/kg on days -3 and -2, tacrolimus 0.03 mg/kg/day starting day -1 with target concentration 5-15 ng/ml and mycophenolate mofetil (MMF) 30 mg/kg/day starting. The MMF was continued until day +30. Tacrolimus was continued until day +100 and gradually tapered over 1 month in absence of GvHD. Steroids were used in this group as the pre-medication to thymoglobulin and graft infusion. In the PTCy group patients received cyclophosphamide 50 mg/kg on days +3 and +4. Mesna 50 mg/kg was administered as 24-hour infusion on the days of cyclophosphamide administration. MMF 30 mg/kg/day was started on day +5 and continued until day +35. Tacrolimus 0.03 mg/kg/day was started on day +5 with target concentration 5-15 ng/ml. Tacrolimus in this arm was in the same way continued until day +100 and gradually tapered over 1 month in absence of GvHD. Use of steroids was prohibited from day-5 to day+5. The rest of the supportive care was the same in both arms. The standard antifungal prophylaxis was fluconazole starting on day 0 and continued until engraftment.

### Clinical outcomes

Time to disease relapse, acute GvHD (GvHD), moderate to severe chronic GvHD (cGvHD), non-relapse mortality (NRM), overall survival (OS), event-free survival (EFS), and GvHD-relapse free survival (GRFS) were defined as the time from transplantation to the event. Incidence of aGvHD was calculated at 125 days after HSCT, and the time frame for the other outcomes was free years. Events for EFS were relapse or death. Events for GRFS were either death, relapse, grades III-IV acute GvHD or systemic therapy-requiring chronic GvHD [12]. Patients were censored at the time of last contact or a second transplantation for all outcomes. Disease relapse was defined as morphologic or cytogenetic evidence of disease with pre-transplantation characteristics. Disease staging, including bone marrow biopsies, was routinely performed on days +30,+60,+100, +180, +365 post-transplant. The Consensus Conference criteria and National Institutes

Table 1. Characteristics of patients

Parameter	Thymoglobulin (n=16)	PTCY (n=17)	P-value
Age, median (range, years)	45 (18-60)	46 (26-57)	0.38
Diagnosis, n	CML 4 CP -3 AP -1 MDS 11 AEB I -1 AEB II -8 MLD -2 MPN unclassifiable 1	CML 8 CP -1 AP -1 BC -2 MDS 8 AEB I -2 AEB II -6 MPN unclassifiable 1	0.41
Male/female, n	6/10	10/7	0.22
High cytogenetic risk	53%	17%	0.11
Female donor	31%	29%	0.90
ABO mismatch, n	None 6 Major 4 Minor 5 Mixed 1	None 7 Major 4 Minor 4 Mixed 2	0.92
CMV serostatus, Donor/recipient, n	-/- 2 -/+ 7 +/+ 7	+/- 2 -/+ 8 +/+ 7	0.25

CML = chronic myeloid leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasm, CP = chronic phase, AP = acceleration phase, BC = blast crisis, AEB – access blasts, MLD – multilineage dysplasia.

of Health criteria were used for aGvHD and cGvHD grading [13, 14]. Primary graft failure was defined as the complete absence of donor chimerism in bone marrow biopsy by day +40. Time to engraftment was calculated as time from HSCT to unsupported neutrophil count > 500/μl and white blood cell count >1000/μl for 3 consecutive days. Toxicity was assessed with CTCAE ver. 4.03. Sepsis and severe sepsis were diagnosed based on International Guidelines for Management of Severe Sepsis and Septic Shock [15]. Invasive mycosis was diagnosed in case of probable or proven infection according to EORTC/MSG guidelines [16]. The threshold for cytomegalovirus (CMV) reactivation was >500 copies/mL. Clinically significant CMV reactivation was defined as >10000 copies/mL. Veno-occlusive disease was diagnosed and graded based on EBMT criteria [17].

## Statistical evaluation

The study primary endpoint was the incidence of primary graft failure. The study was planned to enroll 60 patients, 30 patients in each arm. With the study group size was calculated with 30% margin, 0.65 study power and 0.05 significance using Fisher's criterion. Secondary endpoints were incidence of acute grade II-IV acute GvHD, incidence moderate and severe chronic GvHD, non-relapse mortality, OS, EFS, GFRS, relapse incidence, toxicity and infectious complications. The strata for randomization was a pretransplant assessment of mortality (PAM) score [18]. The stratification was performed using Mann-Whitney U-criterion to achieve the minimal differences in PAM between the study groups.

The final median PAM values were 14.1 (range 7.8-25.2) and 14.1 (6.9-21.9) in the thymoglobulin and PTCY groups, respectively (p=0.98).

Comparison of patient characteristics was performed by Mann-Whitney test. The survival distributions for OS, EFS, GFRS were calculated using Kaplan-Meier methodology. The comparisons were made using the log-rank test. Cumulative incidence analysis with competing risks for aGvHD, cGvHD, relapse incidence and NRM was performed using Gray test. Relapse and NRM were accounted as competing risks. Incidence and severity of complications was compared using Chi-square and Mann-Whitney test. Analyses were conducted in SAS 9.3 (SAS Institute, Inc.).

## Results

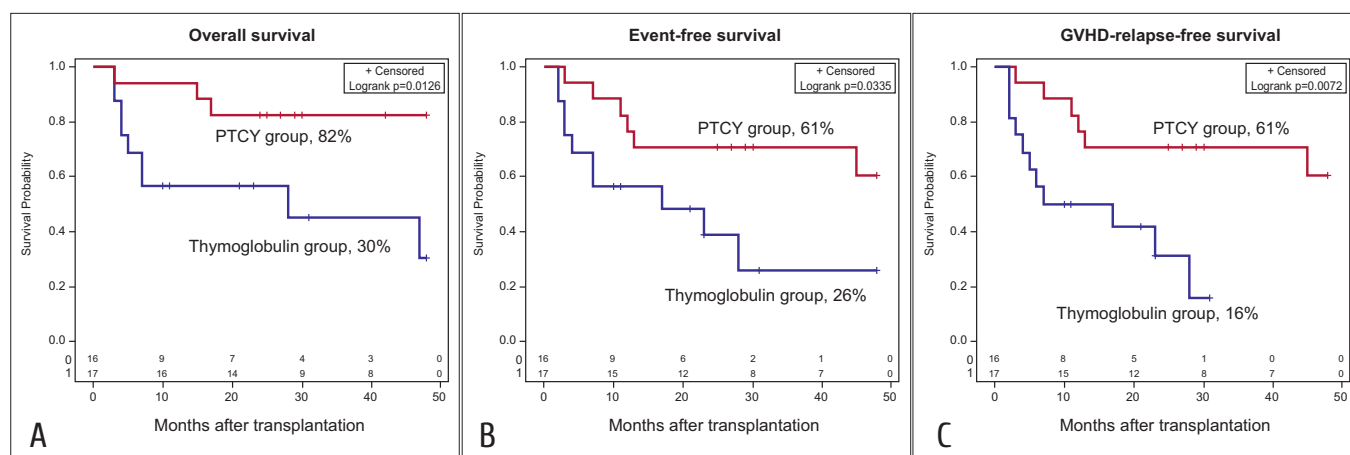
Median follow up in the study was 29 months (range 7-48). There was no difference in the incidence of primary graft failure: 12.50% (95%CI 2%-38%) in the thymoglobulin arm and 11.8% (95%CI 1%-36%) in the PTCY arm, p=0.95. Three out of four patients with primary graft failure died, one was salvaged with second transplantation. All patients without primary graft failure survived to the day of engraftment. Median time to neutrophil engraftment was longer in the PTCY group: 20 (16-33) vs 16 (11-30) days, p=0.0017. Time to white blood cell engraftment was also significantly longer: 21 (16-33) vs 15 (11-30) days, p=0.0016. No differences were observed in the time to platelet engraftment: median 12 (8-40) vs 15 (11-45) days, p=0.1482.

Acute GvHD grade II-IV was documented in 3 (23%) patients in the thymoglobulin group and 1 (6%) patients in the PTCY group ( $p=0.20$ ). No cases of acute GvHD grade III-IV were documented. Moderate and severe chronic GvHD was diagnosed in 3 (23%) patient after thymoglobulin and 4 (25%) patients after PTCY ( $p=0.41$ ). Median time to chronic GvHD was a little shorter after thymoglobulin (5.5 months) compared to PTCY (15 months),  $p=0.11$ . One patient in thymoglobulin and 2 patients in the PTCY group had mild chronic GvHD.

Patients after PTCY prophylaxis had significantly better outcomes of transplantation. 4-year OS was 82% (95%CI 55-94%) vs 30% (95%CI 6-59%),  $p=0.0126$ ; EFS was 61% (95%CI 31-81%) vs 26% (95%CI 5-54%),  $p=0.0335$ , GFRS

61% 95%CI (31-81%) vs 16% (95%CI 1-46%),  $p=0.0072$  (Figure 1). There was a comparable incidence of relapse between the groups (25% vs 29%,  $p=0.77$ ), but significantly reduced non-relapse mortality in the PTCY group (6% vs 38%,  $p=0.0264$ ), which was main cause of the differences in survival outcomes. Primary graft failure and infectious complications were the only causes of non-relapse mortality in the study groups.

No unexpected toxicity was observed during the study. There was no significant difference in the incidence of early complications (Table 2). No cases of neurotoxicity or veno-occlusive disease were documented during the study. The infusion reactions in the thymoglobulin group were allergic reactions and in the PTCY group – one case of cystalgia.



**Figure 1.** Overall (A), event-free (B) and GvHD-relapse-free (C) survival. The percentages shown are 4-year Kaplan-Mayer estimates

**Table 2.** Toxicity and complications observed in ATG and PTCY groups

Parameter	Thymoglobulin (n=16)	PTCY (n=17)	P-value
Liver toxicity grade 2	1 patient	3 patients	0.12
Liver toxicity grade 3	3 patients	0 patients	
Renal toxicity grade 1	6 patients	7 patients	0.78
Renal toxicity grade 2	1 patient	1 patient	
Renal toxicity grade 3	1 patient	0 patients	
TA-TMA	0 patients	1 patient	0.35
Mucositis grade 2	6 patients	4 patients	0.18
Mucositis grade 3	3 patients	2 patients	
Hemorrhagic cystitis grade 2	1 patient	2 patients	0.66
Preengraftment sepsis	2 patients	4 patients	0.52
Preengraftment severe sepsis	0 patients	1 patient	0.36
Invasive mycosis	2 patients	1 patient	0.43
CMV reactivation	7 patients	8 patients	0.87
Infusion reaction	3 patients	1 patient	0.25

**Note:** TA-TMA = transplant-associated microangiopathy. Infusion reaction is defined as any reaction during or immediately after infusion that required change in the systemic therapy.



## Discussion

The study was originally developed to demonstrate if there is a difference in primary graft failure after PTCY. Despite it was terminated prematurely due to poor recruitment, several approximations could be made. We have observed identical number of graft failures in the thymoglobulin and PTCY group. According to CIBMTR data the average number of primary graft failure is 5.5% and CML and MDS patients have the double risk. So the incidence in the current study was not only the same between groups, but almost identical to the one reported by large registry studies [6]. So it is likely that there is no impact of PTCY on the incidence of primary graft failure. On the other hand, we have not observed any positive impact of PTCY on engraftment in this patient population despite previous preclinical data [19]. Unlike primary graft failure engraftment of neutrophils is delayed by several days which in concordance with previously published data [7].

The study was not powered to capture the significance and survival and recruitment was not completed, but most striking results were obtained in terms of survival outcomes. PTCY prophylaxis was associated with significantly higher incidence of OS, EFS and GRFS. The differences were due to reduced non-relapse mortality, it was only 6% in the PTCY group. These extremely low incidence of NRM was recently confirmed in the retrospective [7] and prospective randomized [20] studies. Despite the situation in haploidentical transplantation where PTCY reduces mortality through more effective prevention of acute and chronic GvHD [8], here we observed identical incidence of both acute and chronic GvHD, but the difference was due to late severe bacterial infections. In this study 5 mg/kg dose of thymoglobulin was used which is reported to cause less profound immunosuppression and promote graft-versus-leukemia effect [21, 22]. However the population of MDS and MPN patients is different from acute leukemia. There is a significant iron overload, which may increase the risk of infections after SCT and thymoglobulin effects might overlap with these negative impacts of iron overload [23]. Otherwise this might be an indication of better immunological recovery after unrelated transplantation with PTCY. Additional studies are required to confirm these assumptions.

## Conclusion

Despite incomplete recruitment, this study provides some evidence on the use of PTCY-based prophylaxis for unrelated transplantations in patients with CML, MDS and MPN. The study has demonstrated that there is likely no impact of PTCY on the incidence of primary graft failure. Also it creates the basis for future studies to evaluate survival and immunological recovery in this patient population.

## Conflict of interest

No conflict of interest reported.

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# Рандомизированное исследование тимоглобулина и посттрансплантационного циклофосфана при аллогенной неродственной трансплантации у взрослых с хроническими миелоидными неоплазиями

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## Резюме

В настоящий момент отмечается рост числа публикаций по поводу использования посттрансплантационного циклофосфана (ПТЦФ) в профилактике реакции «трансплантат против хозяина» при неродственной трансплантации гемопоэтических стволовых клеток. Тем не менее, большинство этих публикаций включают только пациентов с острыми лейкозами. Данные о возможности применения ПТЦФ при хроническом миелолейкозе (ХМЛ), миелодиспластическом синдроме (МДС) и хронических миелопролиферативных заболеваниях (ХМПЗ) практически отсутствуют, поэтому в данной популяции пациентов было инициировано проспективное рандомизированное сравнение тимоглобулина и ПТЦФ в профилактике РТПХ при 10/10- HLA совместимой неродственной трансплантации (NCT02627573, clinicaltrials.gov). Стратой для рандомизации был индекс pretransplant assessment of mortality. Исследование было прекращено преждевременно в связи с медленным набором пациентов, тем не менее, за время исследования было включено 33 пациента, 16 пациентов в группу тимоглобулина и 17 пациентов в группу ПТЦФ. Медиана наблюдения составила 29 месяцев. Не было выявлено различий ни в частоте первичного неприживания трансплантата (12,50% против 11,8%,  $p=0,9$ ), ни острой

РТПХ II-IV степени (23% vs 6%,  $p=0,2$ ), ни хронической РТПХ средней и тяжелой степени (25% vs 23%,  $p=0,4$ ) в группах тимоглобулина и ПТЦФ, соответственно. Однако, было в группе ПТЦФ наблюдалась достоверно лучшая общая (82% vs 30%,  $p=0,0126$ ) и бессобытийная (61% vs 26%,  $p=0,0335$ ) выживаемость, а также выживаемость без рецидива и РТПХ (61% vs 16%,  $p=0,0072$ ). Различия были связаны с поздней инфекционной летальностью. Никак достоверных различий в токсичности 2 режимов выявлено не было. Подводя итоги, данное исследование дает обоснование для применения ПТЦФ при неродственных трансплантациях у пациентов с ХМЛ и МДС. Требуются дальнейшие исследования для подтверждения преимущества ПТЦФ над классической профилактикой с тимоглобулином.

## Ключевые слова

Посттрансплантационный циклофосфан, миелодиспластический синдром, хронический миелоидный лейкоз, хроническая миелопролиферативная неоплазия, совместимый неродственный донор.