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Original Article

Comparison of Infectious Complications in Patients Receiving High-Dose Cyclophosphamide as GvHD Prophylaxis After Transplantation From A 9/10 HLA-Matched Unrelated Donor with Standard GvHD Prophylaxis After Transplant From A Fully Matched Related Donor

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Abstract. ***Background*: The aim of this study was to evaluate whether cyclophosphamide administered after allogeneic stem cell transplantation (ASCT) from 9/10 HLA-Matched Unrelated Donors (MMUD) increases the rates of bacterial, fungal, viral infections, complications (hemorrhagic cystitis (HC)), and infection-related mortality compared to allogeneic stem cell transplantation from matched related donors (MRD).**
***Methods*: This is a retrospective multicenter study. 45 MMUD ASCT patients who received posttransplant cyclophosphamide+methotrexate+calcineurin inhibitor compared with 45 MRD ASCT patients who received methotrexate+calcineurin inhibitor.**
***Results*: Although there was a statistically significant prolongation of neutrophil engraftment time in the PTCy arm, there was no statistically significant difference in bacterial infection frequencies between the groups (PTCy; 9 (20%), control; 8 (17.8%), p=0.778). The distribution of CMV infection in the first 100 days was similar (p=0.827), but the distribution of CMV infection rate between the 100th and 365th days was observed more frequently in the control group (p=0.005). HC rates and their grades were similar in both groups (PTCy; 4 (8.8%), control; 6 (13.3%) p=0.502). The rates of VZV infection and invasive aspergillosis were similar in the PTCy and control groups (13.3% in the PTCy and 17.8% in the control group p=0.561). There is also no statistically significant difference in survival analysis (OS, LFS, GRFS, RI, IRM, NRM) between groups. However, the incidence of cGVHD was significantly higher in the control group (P=0.035).**
***Conclusions*: The addition of PTCy to standard GvHD prophylaxis in MMUD ASCT does not lead to an increase in CMV reactivation, bacterial infections, invasive fungal infection, viral hemorrhagic cystitis, or mortality.**

Keywords: Allogeneic hematopoietic stem cell transplantation; cyclophosphamide; hemorrhagic cystitis; infections; invasive fungal infection; post-transplant.

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Introduction. Allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment for various hematologic malignancies, bone marrow failure syndromes, and inherited immunodeficiencies. Despite advances in transplantation techniques, the success of allo-SCT is often limited by complications that remain a significant cause of morbidity and mortality in transplant recipients. Infections remain a major cause of morbidity and mortality in the post-transplant period and are responsible for 35-45% of the causes of death after ASCT.[1-4] According to EBMT 2019 activity survey, 54.1% of deaths in the first 30 days, 33.2% between 30-100 days, 16.5% between 100-400 days, and 12.7% after the first year are due to infections.[5] There are concerns regarding the potential for increased viral infections such as cytomegalovirus (CMV) and BK polyomavirus virus due to the effect of the use of cyclophosphamide-based prophylaxis on immune reconstitution compared to standard Graft Versus Host Disease (GVHD) prophylaxis.[6] Among these infections, CMV reactivation poses a significant clinical challenge due to its association with increased morbidity and mortality. The reactivation of latent CMV infection may lead to an increased risk of CMV-associated disease and opportunistic infection and trigger an increase in the frequency of the BK virüs.[7]

In recent years, post-transplant cyclophosphamide (PTCy) has been increasingly used as a promising strategy to reduce GVHD while potentially preserving the effects of graft versus leukemia (GVL).[8,9] The use of PTCy was first introduced as part of a haploidentical transplant regimen, and subsequent studies have expanded it to other types of SCT, including matched unrelated donor (MUD) and matched related donor (MRD) SCT. In particular, PTCy-based protocols have shown overall survival rates and disease control rates comparable to those achieved with conventional GVHD prophylaxis strategies such as calcineurin inhibitors and methotrexate.[10-13] However, while most studies have demonstrated that PTCy reduces the risk of post-transplant acute and chronic GVHD, its potential impact on the incidence and spectrum of infections has yet to be fully elucidated.

To better understand the impact of PTCy use on infections after allo-SCT, a limited number of studies have investigated the incidence, spectrum, and clinical impact of infectious complications. Overall, the available evidence suggests that PTCy does not significantly increase the risk of infection compared to standard GVHD prophylaxis regimens. A retrospective analysis by Fayard et al. evaluated the incidence of infectious complications after PTCy-based allo-SCT. The study found that bacterial, fungal, and viral infection rates were comparable to those observed with standard GVHD prophylaxis regimens.[14] Another retrospective analysis by Jorge et al. compared single mismatched unrelated donor (MMUD)-PTCy-based regimens with MUD-standard GVHD prophylaxis regimens. The results showed comparable rates of CMV reactivation, invasive pulmonary aspergillosis, and bacterial infection between the two groups.[15] These findings suggest that PTCy does not predispose patients to a higher risk of infectious complications.

However, some articles claim otherwise. Scott et al. reported that according to the Center for International Blood and Marrow Transplant Research analysis, the risk of CMV infection was highest in CMV-seropositive recipients and significantly higher in PTCy recipients, regardless of donor.[16] The potential impact of PTCy on the risk of post-transplant infection remains unclear, and concerns remain. One of the most important reasons for this is that almost all studies on PTCy aim to assess GvHD and disease relapse. The effect on infections has always been a secondary objective. Therefore, no comparative studies are comparing PTCy in MMUD SCT with standard GVHD prophylaxis in MRD SCT concerning infection risk.

In this study, we aimed to compare the rates of bacterial, fungal, viral (CMV, BK, hepatitis) infections, infectious complications (hemorrhagic cystitis, CMV-related graft failure, etc.), and mortality in a specific group of patients (9/10 MMUD) treated with PTCy for GVHD prophylaxis after SCT and MRD patients, treated with standard GVHD prophylaxis.

Materials and Methods.

Study Design and Patient Population. This study is a retrospective registry-based analysis conducted at three Hematopoietic Stem Cell Transplantation (HSCT) centers in Ankara. The study period spans from 2016 to 2022. The study population was adult patients who underwent SCT at an age ≥ 18 years. The PTCy group includes patients with a hematologic malignancy, AML (Acute Myeloid Leukemia), ALL (Acute Lymphoblastic Leukemia), high-grade Lymphoma, or high-risk MDS (Myelodysplastic Syndromes) who received a single-HLA-MMUD graft after a Myeloablative Conditioning (MAC) regimen. The control group comprises 45 patients who received an MRD graft after a MAC regimen with conventional GVHD prophylaxis. The

following criteria were considered for exclusion: the utilization of ATG, ex vivo T-cell depletion, or concurrent implementation of in vivo T-cell depletion. AML and MDS risk classification was made according to the 5th edition of the World Health Organization (WHO) classification of haemato-lymphoid tumors: myeloid and histiocytic/dendritic neoplasms.[17] ALL and lymphoma risk classification was made according to the 5th edition of the WHO classification of haematolymphoid tumors: lymphoid neoplasms.[18]

Conditioning Regimen and GVHD Prophylaxis. All patients included in the study were given the MAC regimen. Within the PTCy group, the two most commonly used MAC regimens were as follows: Fludarabine (Flu) (120 mg/m^2 IV), combined with Total Body Irradiation (TBI) at a total dose of 800-1200 cGy, and Cyclophosphamide (Cy) (120 mg/kg) combined with TBI at similar total dose.

GVHD prophylaxis in the PTCy group involved the administration of Cy at a daily dosage of 50 mg/kg IV on the +3 and +4 days, along with methotrexate (MTX) on the +1st day (15 mg/m^2), +3rd day, and +6th day (10 mg/m^2), as well as tacrolimus (range 5-15 ng/mL), or Cyclosporine A (CyA) at a daily dosage of 3 mg/kg/day initiated on the 5th day. In the absence of significant GVHD, dose discontinuation was implemented around days 90-180. In the control group, patients received conventional GVHD prophylaxis based on calcineurin inhibitors, specifically CyA, from the -1st to the +90-180th day in the absence of GVHD, in addition to Mtx at the +1st day (15 mg/m^2), +3rd day, +6 th day, and +11th day (10 mg/m^2).

Supportive Care And Anti-Infectious Prophylaxis. The patients were followed in the bone marrow transplant unit in isolated rooms with a Negative Vacuum HEPA filter. Surveillance cultures, including rectal swabs, were taken from all patients on admission to the transplant unit. Conditioning regimens were started when patients were admitted to the bone marrow transplant unit. With the initiation of the conditioning regimen, patients received levofloxacin 500 mg/day until engraftment, valacyclovir 2x500 mg/day for 365 days, and fluconazole 2x200 mg/day as long as immunosuppressive therapy continued. In addition, trimethoprim-sulfamethoxazole 800/160/day was started after engraftment and given 3 days a week for a minimum of 1 year after SCT or until immunosuppressive therapy was stopped.

Piperacillin-tazobactam alone was used as empirical treatment for febrile neutropenia 4x4.5 g/day and escalated according to culture and fever response. A de-escalation strategy is applied, especially in patients with septic symptoms. Serum Galactomannan level and CMV-PCR were followed twice a week in the first 30 days after SCT and once a week after the 30th day. In patients with active GVHD, follow-up was continued until immunosuppressive therapy was discontinued. Epstein-Barr virus (EBV) PCR and Adenovirus (ADV) PCR were not routinely performed unless there is clinical suspicion.

Definitions. Infection risk periods were defined in 2 groups as post-transplant between 0.-+30 days (Pre-engraftment) and +31-+100.days (Engraftment). Neutrophil engraftment was accepted as the first of 3 measurement days when the ANC count after ASCT was >500 cells/mm^3, following the lowest level. Neutropenia was defined as absolute neutrophil count (ANC) <500 cells/mm^3. For bacteria colonizing the skin, isolation of the same strain in 2 consecutive blood cultures was rated as Blood Stream Infection (BSI). Isolation of the pathogen from 1 blood culture of a neutropenic patient from the beginning of the conditioning regimen to the completion of the engraftment period was considered Peripheric Blood-BSI (PB-BSI). BSIs were considered polymicrobial when 2 pathogens were isolated from a single blood culture. Any bacterial, viral, or invasive fungal infection (IFI) requiring intravenous therapy or causing hospital stay or prolonging hospital stay was considered severe. CMV-associated end-organ disease was classified according to the guidelines, and viremia requiring pre-emptive therapy was defined as clinically significant infection. Anti-CMV therapy was initiated when the CMV-PCR copy number was >1000 IU/ml in a single measurement or >500 IU/mL in two consecutive measurements. Disseminated Zoster Infection, Viral Pneumonias, and BK-polyomavirus hemorrhagic cystitis (BKV-HC) were also investigated as other viral infections. BKV-HC is defined according to the European Conference on Infections in Leukemia (ECIL) guidelines.[19] Invasive Fungal Infections were classified according to the European Organisation for Research and Treatment of Cancer (EORTC)/MSG Criteria.[20] GVHD: Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were defined according to NIH criteria.[21] Overall survival (OS) was calculated as the time to last follow-up or time to death after transplantation. Leukemia-free survival (LFS) was defined as the time from allo-SCT to death or relapse, whichever came first. Graft-versus-host relapse-free survival (GRFS) was defined as the time without disease relapse/progression or GVHD after allo-SCT. Relapse incidence (RI) was compared between arms separately.

Infection-related mortality (IRM) was defined as death that was thought to be caused by a serious infection during the follow-up period without relapse/relapse or GVHD. Non-Relapsed Mortality (NRM) was calculated as the time from transplantation to death due to any cause other than relapse. BSI-related mortality was defined as the mortality that developed within the first seven days after the blood culture became positive.

Ethics Committee Approval. Before the treatment, the patient's written consent for treatment and data use were obtained. The study was initiated with the approval of the ethics committee of Gulhane Training and Research Hospital (2021/8).

Statistical Analysis. Data were analyzed using the IBM SPSS 21 (IBM SPSS Inc, Chicago, IL) software package. The statistical significance level was set at 0.05. For descriptive statistics, continuous data were summarized using the mean and standard deviation, while categorical data were presented as frequencies and percentages. The normal distribution compatibility of variables was assessed using the Kolmogorov-Smirnov test, and the homogeneity of variances was examined with Levene's test. The distribution of categorical variables among the groups was evaluated through Pearson's chi-square test and Fisher's exact test. Group means of normally distributed continuous variables were compared using Student's t-test, while non-normally distributed variables were compared using the Mann-Whitney U test. The relationship between categorical variables was assessed using Phi and Cramér V correlation coefficients. Survival rates as OS, LFS, GRFS, NRM, IRM/BSI-related mortality in the PTCy and control groups were calculated using Kaplan-Meier survival analysis. The survival of the PTCy and control groups was evaluated using the Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware methods.

Results.

Patient Characteristics. In our study, a total of 90 patients (n: PTCy: 45, Control: 45) were included, with 60 (67%) being male and 30 (33%) being female. The participants' mean age was 40.17±14.72 (ranging from 18 to 68) years. Table 1 provides additional characteristic features. When analyzing factors such as gender, age, disease distribution, number of treatment lines, previous transplant history, pre-transplant disease status, and disease stages before transplantation, no statistically significant differences were observed between the PTCy and control groups. The median follow-up period was 30 (5-74) months in the PTCy arm and 21.16 (5-125) months in the control arm (**Table 1**).

Comparison of Transplantation Data. **Table 2** illustrates that there was no statistically significant difference in the mean CD34+ cell count between the PTCy group (5.24±1.41) and the control group (5.32±1.39) (p=0.871). In addition, there was also no statistically significant

Table 1. Demographic data of the groups and comparison of distributions.

Patient Characteristics:		**PTCy (n=45)**	**Control (n=45)**	**Test, Statistics**
Gender	**Female**	16 (38.1%)	14 (37.8%)	$\chi2$=0.189* p=0.664
	Male	26 (61.9%)	23 (62.2%)	
Age (years) (Mean± SS)		40.73±15.57	39.62±13.97	t=0.356** p=0.723
Diagnosis	***AML***	24 (53.4%)	24 (53.4%)	$\chi2$=2.043* P=0.563
	ALL	10 (22.2%)	14 (31.1%)	
	MDS	6 (13.3%)	5 (11.1%)	
	Lymphomas	5 (11.1%)	2 (4.4%)	
Number of Treatment Lines up to Transplantation	***1***	14 (31.1%)	10 (22.2%)	$\chi2$=1.451* P=0.694
	2	17 (37.8%)	22 (48.9%)	
	3	10 (22.2%)	10 (22.2%)	
	≥4	4 (8.9%)	3 (6.7%)	
Previous Transplant History	***Allogeneic SCT***	1 (2.2%)	2 (4.4%)	$\chi2$=2.345* P=0.310
	Autolog SCT	2 (4.4%)	0	
Pre-Transplant Disease Status	***CR1***	31 (68.9%)	30 (66.7%)	$\chi2$=0.069* P=0.995
	CR2	9 (20%)	10 (22.2%)	
	CR3	1 (2.2%)	1 (2.2%)	
	Refractory	4 (8.9%)	4 (8.9%)	
Disease Stage	***Intermediate Risk***	11 (24.4%)	9 (20%)	$\chi2$=0.257* P=0.612
	High Risk	34 (75.6%)	36 (80%)	
Median Time of Transplant (Month)		16 (0-66)	12.36 (0-49)	U=893*** P=0.334
Median Follow-up Time (Month)		30 (5-74)	21.16 (5-125)	U=825*** P=0.130

* Pearson Chi-square test statistic value. **Student-t test statistical value. *** Mann-Whitney U test statistics value.

Table 2. Comparison of transplantation data.

		PTCy (n:45)	Control (n:45)	Test, Statistics
CD34 (Mean ± SS)		5.24±1.41	5.32±1.39	U=992* p=0.871
TNC (Mean± SS)		9.91±4.58	10.69±3.89	U=844.50* p=0.175***
Stem Cell Source	**Bone Marrow(BM)**	4 (8.8%)	2 (4.4%)	$\chi2$=0.715** P=0.699
	Peripheral Blood (PB)	40 (88.9%)	42 (93.4%)	
	PB+BM	1 (2.2%)	1 (2.2%)	

* Mann-Whitney U test statistics value. **Pearson Chi-square tes tstatistical valuee. ***Significant difference was found at 0.05 Significance level.

Table 3. Comparison of donor and recipient pre-transplant viral serologies in groups.

	Donor	Recipient	PTCy (n=45)	Control (n=45)	Test, Statistics
CMV-IgG Status	-	+	11 (24.4%)	6 (13.3%)	$\chi2$=2.693* p=0.260
	+	+	34 (75.6%)	38 (84.5%)	
	+	-	0	1 (2.2%)	
	-	-	0	0	
EBV-IgG Status	-	+	5 (11.1%)	6 (13.3%)	$\chi2$=2.853* p=0.415
	+	+	35 (77.8%)	29 (64.53%)	
	+	-	4 (8.9%)	6 (13.3%)	
	-	-	1 (2.2%)	4 (8.9%)	
Anti HBc-IgG Status	-	+	4 (8.9%)	5 (11.1%)	$\chi2$=1.568* p=0.667
	+	+	1 (2.2%)	0	
	+	-	4 (8.9%)	6 (13.3%)	
	-	-	36 (80.0%)	34 (76.6%)	

* Pearson Chi-square test statistic value.

difference in the mean TNC value between the PTCy group (9.91±4.58) and the control group (10.69±3.89) (p=0.175). The distribution of stem cell sources was found to be similar in both the PTCy and control groups (p=0.699), with the majority of patients in both groups receiving a "peripheral" stem cell source.

Comparison of Pre-Transplant Viral Serologies. The distribution of CMV-IgG and EBV IgG status in donor and recipient in both Post-Cy and control groups was similar. It was observed that both donor and recipient CMV IgG positivity constituted the majority of the frequency (75.6%-84.5%). The same was true for EBV IgG serology (77.8%, 64.5%). Anti-HBc-IgG status distributions were similar in the PTCy and control groups (P=0,667), and the rate of both donor and recipient negative status were majority in both groups (PTCy; 36 (80.0%), control; 34 (76.6%)) (**Table 3**). HBsAg, Anti HCV, and Anti HIV serology results of all patients or donors were negative. Preemptive antiviral treatment (tenofovir or entecavir) was started if any donor or recipient had a positive AntiHBcIgG serology. Hepatitis B reactivation was not observed in any patient during the transplant period and the following one-year follow-up.

Comparison of GVHD rates, Viral Reactivation, Infections, and Survival Data After Transplantation. Frequency distributions of aGVHD in the PTCy and control groups were similar (p=0.037). Moreover, the incidence of cGVHD was significantly higher in the control group (28.9%, n=13) compared to the PTCy group (11.1%, n=5). Frequency distributions of febrile neutropenic (FEN) in the PTCy and control groups were similar (p=0.391). It was observed that those who had ‘’1’’FEN in the first 30 days in both groups were in the majority (PTCy; n:32 (71.1%) and control; 25 (55.6%). There was no statistically significant difference in BSI frequencies between the PTCy arm and the control arms. The distribution of CMV infection in the first 100 days was similar in the PTCy and control groups (p=0.827). The distribution of CMV infection rate between the 100th and 365th days in the PTCy and control group was statistically significant, and it was observed more frequently in the control group. (PTCy; 4(8.8%), control; n:12(26.7%) (p=0.027). HC rates and their grades were similar in the PTCy and control groups (p=0.502). The rate of HC was n:4 (8.8%) in the PTCy group and n:6

Table 4. Comparison of data after transplantation.

		PTCy (n:45)	Control (n:45)	Test, Statistics
Neutrophil Engraftment Time (day) (Mean ± SD)		18.25±4.63	15.9±6.22	U=526.00* P<0.002***
Platelets Engraftment Time (day) (Mean± SD)		18.41±4.71	15.86±9.31	U=443.50* P<0.001***
Acute GvHD	**No**	28 (62.2%)	32 (71.1%)	$\chi2$=0.800** P=0.371
	Yes	17 (37.8%)	13 (28.9%)	
Chronic GvHD	**No**	40 (88.9%)	32 (71.1%)	$\chi2$=4.444** P=0.035
	Yes	5 (11.1%)	13 (28.9%)	
Febrile Neutropenia (FEN) Episodes Count	**0**	1 (2.2%)	5 (11.1%)	$\chi2$=4.112** P=0.391
	1	32 (71.1%)	25 (55.6%)	
	2	9 (20%)	10 (22.2%)	
	≥3	3 (6.7%)	5 (11.1%)	
Bloodstream Infections (BSIs)		9 (20%)	8 (17.8%)	$\chi2$=0.073** P=0.788
CMV Infection +1.<-->+100.day	**No**	28 (62.2%)	29 (64.4%)	$\chi2$=0.048** P=0.827
	Yes	17 (37.8%)	16 (35.6%)	
CMV Infection +101. <-->+365.day	**No**	41 (91.2%)	33 (73.3%)	$\chi2$=4.865** P=0.027***
	Yes	4 (8.8%)	12 (26.7%)	
Haemorrhagic Cystitis	**No**	41 (91.1%)	39 (86.7%)	$\chi2$=0.450** P=0.502
	Yes	4 (8.8%)	6 (13.3%)	
Haemorrhagic Cystitis Grade	**No**	41(91.2%)	39 (86.7%)	$\chi2$=2.85** P=0.415
	1	2 (4.4%)	2 (4.4%)	
	2	1 (2.2%)	3(6.7%)	
	3	1 (2.2%)	1 (2.2%)	
	4	0	0	
VZV Infection	**No**	44 (97.8%)	43 (95.6%)	$\chi2$=0.345** P=0.557
	Yes	1 (2.2%)	2 (4.4%)	
Invasive Fungal Aspergillosis	**No**	39 (86.7%)	37 (82.2%)	$\chi2$=0.338** P=0.561
	Yes	6 (13.3%)	8 (17.8%)	

* Mann-Whitney U test statistics value. **Pearson Chi-square tes tstatistical valuee. ***Significant difference was found at 0.05 Significance level.

Table 5. Correlations between Donor/Recipient CMV serology status and CMV infection.

	CMV infection +1.<--> +100.day		CMV infection +101.<--> +365.day	
	r (ϕ)*	**p**	**r (ϕ)***	**p**
Donor/Recipient CMV serology status	-0.007	0.944	-0.082	0.443
Acute GVHD rate	0.252	0.102	0.189	0.220
Chronic GVHD rate	0.137	0.375	0.057	0.710

*Phi correlation coefficient.

(13.3%) in the control group. The rates of VZV infection and invasive aspergillosis were similar in the PTCy and control groups (**Table 4**).

No statistically significant association was observed between CMV infection observed both within the first 100 days and between days 101-365 and donor/recipient CMV serology status, aGVHD, and cGVHD (**Table 5**).

In the PTCy arm, 6 patients died due to infections (n:4 bacterial septic shock, n:2 CMV pneumonia. In the control group, 6 patients died due to BSI septic shock and 2 due to Covid-19-related infection. There was no statistically significant difference in IRM between both groups. When evaluated in terms of OS, no statistically significant difference was found between PTCy and control groups. Median OS for PTCy: 56 months (Range 0-66), and control: 38 months (Range 0-49)(p=0.664) (**Figure 1**). Leukemia Free Survival calculation included 34 patients in the PTCy arm and 38 patients in the control

Table 6. Comparison of Survival Data.

	PTCy (n=45)	Control (n=45)	Test, Statistics
Infection Related Mortality	6 (13.3%)	8(17.8%)	$\chi2$=0.338* P=0.561
Non Relaps Mortality	8 (17.8%)	9(20.0%)	$\chi2$=0.073* P=0.788
Relapse Incidence	9 (20.0%)	11 (%24.4)	$\chi2$=0.257* P=0.612
Overall Survival (Median) (Month)	56 (0-66)	38 (0-49)	$\chi2$=0.189* P=0.664
Leukemia Free Survival (Median) (Month)	18 (1-66)	7.83 (1-49)	$\chi2$=1.442* P=0.230
Graft-Versus-Host Relapse Free Survival (Median) (Month)	3 (1-57)	5 (1-49)	$\chi2$=0.11* P=0.915

* Pearson Chi-square test statistic value.

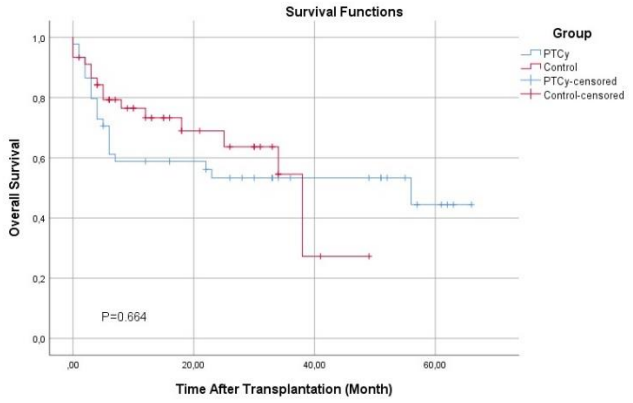

Figure 1. Overall survival chart.

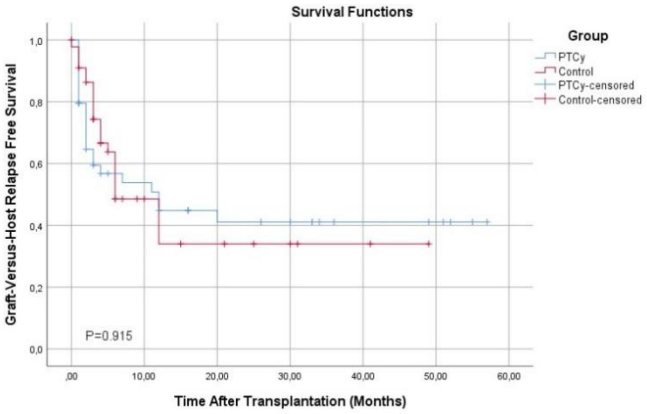

Figure 2. Graft-Versus-Host relapse free survival chart.

arm, and no statistically significant difference was found between the two arms (P=0.230, 18 months in PTCy vs 7.83 months in the control group). The RI was similar in both groups (P=0.612) and found to be 20.0% vs 24.4% in PTCy and control groups, respectively. Also, NRM rates were similar in both groups (P=0.788) and found to be 17.8% vs. 20.0% in PTCy and control groups, respectively (**Table 6**). The median GRFS time was 3 months (Range 1-57) and 5 months (Range 1-49) for PTCy and control, respectively, and no statistically significant difference was found between the two arms (p=0.915) (**Figure 2**).

Discussion. PTCy is widely used and has shown promise in reducing the incidence and severity of GVHD without compromising GVL efficacy. PTCy minimizes the risk of GVHD by selectively reducing alloreactive T cells while preserving other immune cell subsets, such as regulatory T cells (Tregs) and memory T cells, which are crucial for immune reconstitution. However, concerns remain about the potential impact of PTCy on the risk of infection. Few studies have directly compared the incidence of all bacterial, viral, and fungal infectious complications in patients receiving PTCy-based regimens with patients receiving conventional GVHD prophylaxis protocols. These studies have predominantly compared CMV infection and BK virus HC. In this study, we found that PTCy did not lead to an increased risk of infection with all pathogens (bacterial, viral, and fungal) compared to standard GVHD prophylaxis protocols. Moreover, when specific types of infections were analyzed as CMV and BK virus-related HC, we also found that PTCy did not demonstrate an increased risk compared to standard protocols.

PTCy-based regimens, like those for patients receiving other standard GVHD prophylaxis, often require prophylactic antimicrobial agents and close monitoring to reduce the risk of infection. No significant increase in the risk of infection was observed, as shown in many other studies, including our study. IRM rates between 9% and 20% have been reported in large PTCy studies.[22-25] Similar rates were reached in our study, 13.3% in the PTCy arm and 17.8% in the control arm, with no statistically significant difference. IRM is more frequent due to bacterial causes and was observed more frequently in the pre-engraftment period. Gram-negative bacilli was the most common bacterial pathogen detected in both groups. In a prospective study by Jorge et al., the incidence of BSI, a common and serious complication after allo-SCT, was compared between patients receiving PTCy and those receiving standard prophylaxis. The study found similar rates of BSI in both groups (12% in the PTCy MMUD group versus 20% in the MUD group), suggesting that PTCy did not predispose patients to this particular type of infection.[15] Although prolonged

neutropenia and endotoxin-induced mucositis are risk factors that may lead to an increase in the frequency of BSI, the frequency of BSI in our study was similar between both arms (20.0% in the PTCy arm and 17.8% in the control arm) and is similar to the data in the literature (16% to 40%).[26] This suggests that with PTCy, additional prophylaxis is not needed to offset the potential immunosuppressive effects of the drug effectively. However, there are also studies reporting the opposite. One of them reported that PTCy leads to an increase in the frequency of infection due to prolonged CD4 recovery time and is associated with lower overall survival.[27] In another study, the addition of PTCy to Haplo-HCT was shown to have an increased incidence of post-transplant IRM compared to single Ag-MMUD-HCT.[28]

BK virus reactivation after allogeneic HSCT is common (5-68%) and is associated with clinical findings ranging from asymptomatic viruria to severe HC.[29-31] aGVHD, mycophenolate exposure, cord blood HSCT, and PTCy were the most important determinants of BK virus reactivation.[7,30] Studies have also concluded that the slower immune recovery of HLA mismatched HCT leads to an increase in viral infections, which is claimed to contribute to the difference in the incidence of HC.[32-34] In our study, neutrophil engraftment time was statistically significantly longer in patients who underwent PTCy compared to control. We expected a higher incidence of BK virus reactivation and HC in the PTCy arm due to prolonged neutropenia and cyclophosphamide exposure. However, the frequency of BK virus reactivation and HC after allo-SCT was observed at a lower frequency compared to previous studies, and no difference was observed between the PTCy group and the control group. This may be due to prolonging the duration of classical mesna administration and increasing hydration. In a study by Mac et al., the duration of mesna administration was extended until 24 hours after the completion of PTCy, and hydration was increased. Thus, the total incidence of HC in the first 100 days was 31.4%, the rate of grade 3 HC was 11.5%, and no patient had grade 4 HC. The fact that these results were similar to those in our study suggests that mesna application time and hydration affect HC.[35] In terms of HLA mismatch, Al Malki et al., also reached a similar conclusion to our findings. They found similar incidence and severity of HC when they compared haploidentical HCT with MMUD HCT.[33,36] This situation may make BK virus reactivation and HC, which is one of the important obstacles to PTCy preference, an acceptable risk factor.

Reactivation of latent CMV infection and the adverse effect of antiviral therapies used during treatment on stem cells after allo-SCT may lead to significant morbidity, including engraftment failure syndrome and increased risk of CMV-related diseases and opportunistic infections. To better understand the relationship between PTCy and CMV reactivation, several studies have investigated the incidence, risk factors, and clinical implications of CMV reactivation in patients receiving PTCy-based allo-SCT regimens.[16] These studies evaluated the impact of PTCy on the timing of CMV reactivation, its association with GVHD, and overall outcomes in terms of morbidity and mortality. PTCy was shown to be an independent risk factor for CMV in this study.[16] In our study, there was no significant difference in CMV serostatus between the two arms, and donor/recipient CMVIgG +/+ status accounted for the majority of participants. However, CMV serostatus has a guiding role in the choice among multiple potential donors; in particular, CMV reactivation was associated with inferior survival outcomes in allo-SCTs with donor/recipient CMVIgG -/+ serostatus in a previous study.[37] The most important reason for the statistically higher frequency of CMV reactivation in the control group between days +101-365 in our study is that the frequency of cGVHD was also more frequent in the control arm.

Interestingly, we could not show a statistically significant association to support this argument. No statistically significant association was found between cGVHD and CMV reactivation between days +101-365. In addition, most retrospective analyses, including our study, cover the period before the prophylactic use of letermovir in patients undergoing allo-HCT. Currently, letermovir during allo-HCT has shown very promising results in preventing CMV viremia.[38,39]

The incidence of invasive fungal infections, such as invasive aspergillosis, did not differ significantly between PTCy-based regimens and conventional protocols in our study (13.3% in the PTCy arm and 17.8% in the control arm). Although this rate is generally higher than other studies (<%10), it is thought to be related to prolonged steroid use and history of IFI before transplantation.[3,40,41]

Although PTCy does not appear to increase the risk of infection, it is important to note that close monitoring and appropriate management of infections in allo-SCT recipients remains important regardless of the GVHD prophylaxis regimen used. Prompt diagnosis and timely initiation of appropriate antimicrobial therapy are essential to optimize patient outcomes. Larger, well-designed, prospective studies with longer follow-up periods are needed to elucidate further the impact of PTCy on infectious outcomes after allo-SCT.

In terms of other survival analyses, our study showed that PTCy did not lead to an increase in the incidence of relapse as in another study[42-44] and did not have a negative effect on overall survival. These data support the idea that a single-HLA-MMUD HSCT using PTCy may be a suitable alternative for patients without HLA-matched donors.

The data obtained from our study suggest that in the absence of MRD, single Ag-MMUD-HCT may be a good alternative by addition of PTCy and may lead to similar survival results. While this study provides valuable insights, there are some limitations, primarily due to the retrospective nature of the analysis. Although the follow-up period is adequate in terms of infections, the general follow-up period is short. The risk of infection is influenced by multiple factors, including the patient's underlying disease, treatments, remission status, pre-transplant infection status, preparation regimen, and post-transplant immune reconstitution. Although a very isolated group of participants was selected in our study, other risk factors in terms of infections may have affected the results.

Conclusions. In summary, our findings suggest that the use of PTCy as GVHD prophylaxis in allo-SCT from a single Ag-MMUD does not lead to a substantial increase in the risk of CMV reactivation, bacterial infection, invasive fungal infection, or viral hemorrhagic cystitis when compared to conventional GVHD prophylaxis regimens from MRD. Implementation of preventive measures and close monitoring of patients, regardless of PTCy, can help reduce the risk of infection-related mortality.

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