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Post Transplant Cyclophosphamide vs Thymoglobulin in MMUD Transplantation Journal Club

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Post-transplant Cyclophosphamide Versus Thymoglobulin in HLA-Mismatched Unrelated Donor Transplant for Acute Myelogenous Leukemia and Myelodysplastic Syndrome

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Learning Objective

Compare and contrast the utility of post-transplant cyclophosphamide (PTcy) versus thymoglobulin for graft versus host disease (GVHD) prophylaxis in mismatched unrelated donor (MMUD) transplantation

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Matching Human Leukocyte Antigen (HLA) Genes

- Gold standard is HLA genotypically identical sibling donors
  - Only available in 30% of patients
- Pharmacologically overcome HLA mismatch

serotypes (~100)	6	9	19	46	10	21
alleles (>14,000)	673	955	1,977	4,179	2,902	3,356
proteins (>10,000)	539	648	1,444	3,095	2,067	2,372

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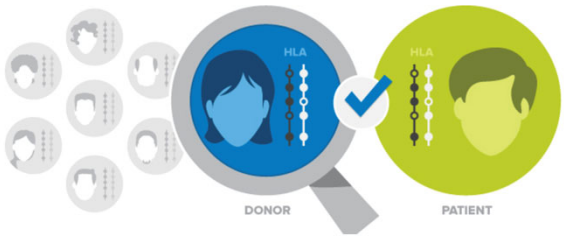
Tiercy JM. Haematologica. 2016;101(6):680-687.

Mismatched Unrelated Donor Transplants

- MMUD transplants at one or several major histocompatibility complex alleles have resulted in:
  - Increased risk of GVHD
  - Higher non-relapse mortality (NRM)
  - Reduced relapse-free survival (RFS)
  - Adverse overall survival (OS)



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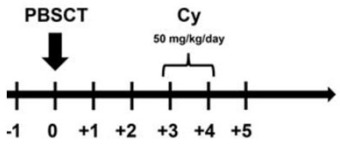
Tiercy JM. Haematologica. 2016;101(6):680-687.
Schönemann HJ, et al. Blood Advances. 2018;2(22):3198-3225.

Pharmacologic Options

- Thymoglobulin depletes T cells primarily through complement-dependent cell lysis
- PTcy selectively depletes rapidly proliferating alloreactive T cells while sparing the memory T cells
  - Lower rates of graft failure, severe acute GVHD, and chronic GVHD in haploidentical BMT (haploBMT)



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Schönemann HJ, et al. Blood Advances. 2018;2(22):3198-3225.

Previous Trial

PTcy in haploBMT	
Objective	Evaluate the safety and efficacy of PTcy to prevent GVHD after nonmyeloablative conditioning and haploBMT from partially HLA-mismatched related donors
Methods	Retrospective chart review of 68 patients Patients with high-risk hematologic malignancies for whom standard HLA-matched, related, or unrelated was unavailable or inappropriate
Intervention	PTcy 50 mg/kg IV on day 3 or on days 3 and 4
Primary Outcome	Engraftment, incidence and severity of GVHD, and NRM
Primary Outcome Result	• Graft rejection occurred in 9 out of 66 patients (13%) • Grades II-IV and III-IV aGVHD by day 200 were 34% and 6%, respectively • Probabilities of non-relapse mortality at 100 days and at 1 year after transplantation were 4% and 15%
Conclusion	PTcy was associated with acceptably low fatal graft rejection, aGVHD, and cGVHD, while allowing prompt engraftment

Luznik L, et al. Biology of Blood and Marrow Transplantation. 2008;14(6):641-650.

Previous Trial

PTcy vs thymoglobulin for GVHD prophylaxis in MMUD	
Objective	Compare outcomes of PTcy vs anti-thymocyte globulin (ATG) as GVHD prophylaxis in patients receiving MMUD bone marrow transplantation
Methods	• Retrospective study from European Society for Blood and Marrow Transplantation (EBMT) • 1001 and 102 patients receiving ATG or PTcy, respectively • Diagnosed with AML • Undergoing first allo-HSCT from a 9/10 MMUD
Intervention	ATG: 6 mg/kg (range, 2.5-15) PTcy: variable dose
Primary Outcome	Cumulative incidence of GVHD
Primary Outcome Result	PTcy was associated with a significantly lower incidence of grade III-IV aGVHD (9% vs 19% in the ATG group, p< 0.04)
Conclusion	PTcy is a valid and safe strategy for preventing aGVHD Non-uniform use of immunosuppressive agents

Battipaglia G, at al. Blood. 2019;134(11):892-899.

Study Design

- Single center retrospective chart review
- January 2006 - June 2019
- Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan

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Population

- Patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)
- 7/8 MMUD defined as one antigen or allele mismatch at HLA-A, -B, -C or -DRB1
- GVHD prophylaxis of either PTcy or thymoglobulin in combination with tacrolimus and mycophenolate mofetil

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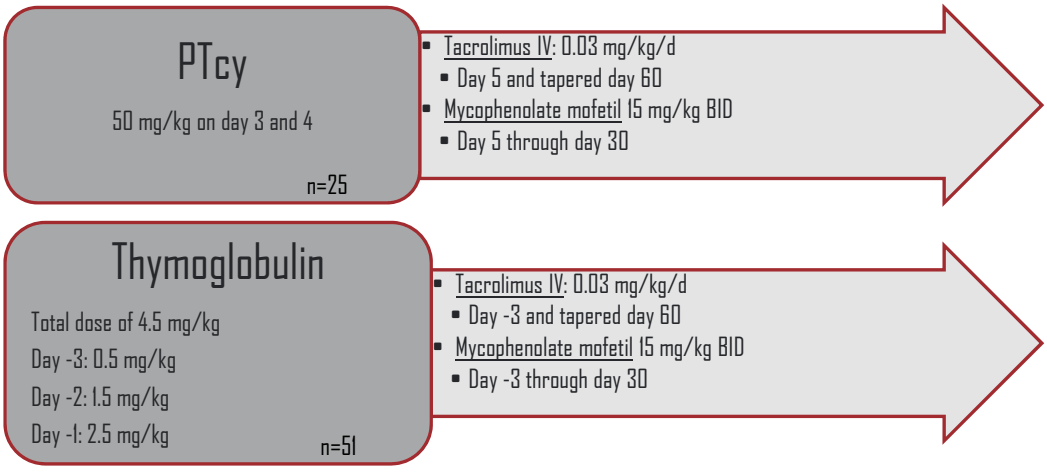
Interventions



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Outcomes

- Primary: estimate the cumulative incidence of acute and chronic GVHD between both groups
- Secondary: assess overall survival (OS), relapse rate, non-relapse mortality (NRM), relapse-free survival (RFS), and GVHD-free relapse-free survival (GRFS) between both groups

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Statistical Analysis

- Fisher's exact test and Wilcoxon rank sum tests were used to compare the 2 groups for categorical and continuous variables, respectively
- Kaplan-Meier estimates were used to summarize the distributions of RFS, OS, and GRFS
- Propensity score-based multivariable analyses (PSCA) were performed to adjust confounding effects of patient characteristics between both groups

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Results

- 76 adult patients with AML or MDS who underwent 7/8 HLA-MMUD transplantation
  - 25 patients received PTcy
  - 51 received thymoglobulin
- Conditioning Regimens
  - Myeloablative conditioning regimen included:
    - Busulfan/ Fludarabine
  - Reduced-intensity conditioning regimens included:
    - Busulfan/ Fludarabine/ TBI
    - Fludarabine/ Melphalan/TBI

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Results

	PTcy (n=25)	Thymoglobulin (n=51)	All (N=76)	p
Age- median (range)	62 (31,76)	53 (22,80)	57 (22-80)	.040
Sex- no (%)				>.99
Male	13 (52)	27 (53)	40 (53)	
Female	12 (48)	24 (47)	36 (47)	
Comorbidity Score (median, range)	2 (0,9)	2 (0,7)	2 (0,9)	.455
Disease, no. (%)				> 0.99
AML	19 (76)	40 (78)	59 (78)	
MDS	6 (24)	11 (22)	17 (22)	
AML subtype, no. (%)				.207
De-novo	12 (63)	32 (80)	44 (75)	
Secondary	7 (37)	8 (20)	15 (25)	

Predominately older, Caucasian male patients

~75% of patients had AML

Shorter follow up for the PTcy group (1.13 years vs 5.27 years)

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Results

	PTcy (n=25)	Thymoglobulin (n=51)	All (N=75)	p
Conditioning Regimen- no.(%)				.002
Myeloablative	5 (20)	30 (59)	35 (46)	
Non-myeloablative	20 (80)	21 (41)	41 (54)	
Graft source, no. (%)				>.99
Bone marrow	1 (4)	2 (4)	3 (4)	
Peripheral blood stem cells	24 (96)	49 (96)	73 (96)	

Non-myeloablative conditioning was more common in the PTcy group

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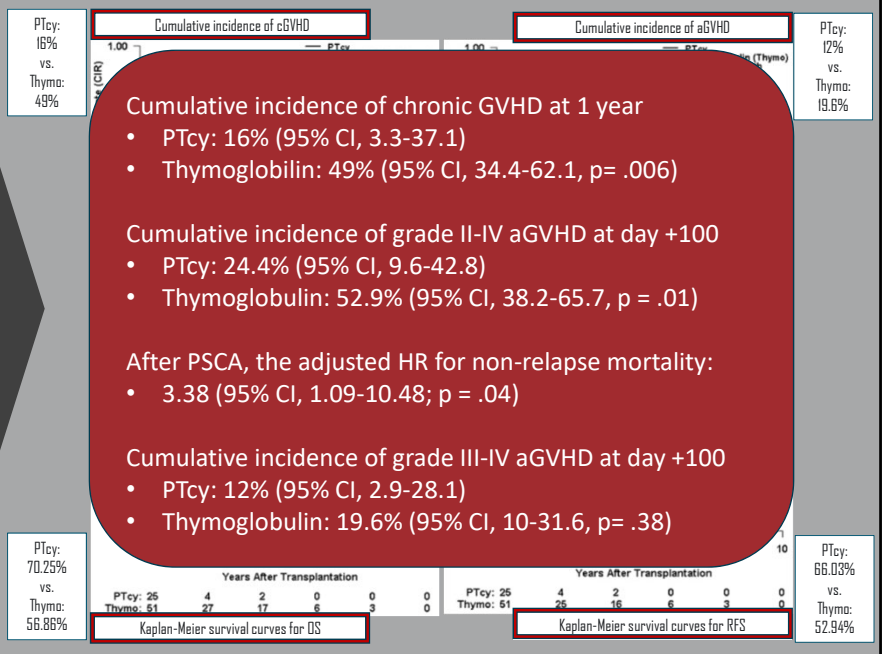
Results

Cumulative incidence of chronic GVHD at 1 year
- PTcy: 16% (95% CI, 3.3-37.1)
- Thymoglobilin: 49% (95% CI, 34.4-62.1, p= .006)

Cumulative incidence of grade II-IV aGVHD at day +100
- PTcy: 24.4% (95% CI, 9.6-42.8)
- Thymoglobulin: 52.9% (95% CI, 38.2-65.7, p = .01)

After PSCA, the adjusted HR for non-relapse mortality:
- 3.38 (95% CI, 1.09-10.48; p = .04)

Cumulative incidence of grade III-IV aGVHD at day +100
- PTcy: 12% (95% CI, 2.9-28.1)
- Thymoglobulin: 19.6% (95% CI, 10-31.6, p= .38)



Results

- Median time to neutrophil engraftment
  - PTcy: 15 days
  - Thymoglobulin: 11 days, p < .001
- Median time to platelet engraftment
  - PTcy: 21 days
  - Thymoglobulin: 15 days, p = .002

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Results

- At 1 year, the relapse rate was:
  - PTcy: 17% (95% CI, 5.1-34.8)
  - Thymoglobulin: 15.7% (95% CI, 7.2-27.1, p = .77)
- Rate of CMV reactivation
  - 20% for PTcy and 43% for thymoglobulin (p = .07)
  - Median time to CMV reactivation was:
    - 39 days after transplantation for PTcy
    - 29 days after transplantation for thymoglobulin (p = .02)

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Author's Discussion

- PTcy was associated with significantly reduced rates of:
  - Grade II-IV aGVHD
  - cGVHD
  - Non-relapse mortality
- Similar incidence of grade III-IV aGVHD in both groups
- Using PSCA, no difference in overall survival, relapse, relapse-free survival, and GVHD-free relapse-free survival was seen between groups
- Further studies involving large patient population are warranted to validate these results

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Questions to Consider

- Did this study include enough patients to achieve the power to accurately detect an effect on GVHD?
- Why were grade II-IV and grade III-IV aGVHD only reported?
- If the PTcy group had the same length of follow up, would it change the results?
- Could the different conditioning regimens in each group significantly alter the results?

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Conclusions

- MMUD transplantations are common and require intensified immunosuppression to reduce GVHD, graft failure, and death
- In patient receiving a 7/8 HLA-MMUD transplants for AML or MDS, PTcy is a viable option to lower rates of acute and chronic GVHD and NRM compared to thymoglobulin
- Further studies should be completed to confirm these results

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Question 1

PTcy was associated with significantly reduced rates of:

a) Grade II-IV acute GVHD
b) Chronic GVHD
c) Non-relapse mortality
d) All the above

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Question 1

PTcy was associated with significantly reduced rates of:

a) Grade II-IV acute GVHD
b) Chronic GVHD
c) Non-relapse mortality
d) All the above

Question 2

There was a statistically significant difference in overall and relapse-free survival noted between PTcy and thymoglobulin.

a) True
b) False

Question 2

There was a statistically significant difference in overall and relapse-free survival noted between PTcy and thymoglobulin.

a) True
b) **False**

Questions?